CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125276Orig1s112

Trade Name: **Actemra**

Generic Name: **Tocilizumab**

Sponsor: **Genentech, Inc.**

Approval Date: 05/22/2017

Indications: ACTEMRA (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

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

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

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.

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125276/S-112

SUPPLEMENT APPROVAL

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

Attention: Karen Robertson
Program Director, Regulatory

Dear Ms. Robertson:

Please refer to your Supplemental Biologics License Application (sBLA), dated November 23, 2016, received November 23, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Actemra (tocilizumab) Injection for intravenous use, 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL.

This Prior Approval supplemental biologics application provides for the alignment of the common prescribing information for two routes of administration of Actemra by adding the labeling changes proposed for BLA 125472/S-024 Actemra SC for the new indication of treatment of adult patients with giant cell arteritis (GCA).

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information, text for the 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

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 Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
05/22/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 use
injection, for 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 (1.2)	May/2017
Dosage and Administration (2.2, 2.6, 2.7, 2.8)	May/2017
Adverse Reactions (6.3)	May/2017
Clinical Pharmacology (12.3)	May/2017
Clinical Studies (14.3)	May/2017

---------- 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.

Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.3)
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.4)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

----------DOSAGE AND ADMINISTRATION----------
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 (IV) 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 (SC) 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 (SC) 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 SC formulation is not intended for intravenous administration.

Polyarticular Juvenile Idiopathic Arthritis (2 3)

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

Systemic Juvenile Idiopathic Arthritis (2.4)

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

General Dosing Information (2.5)
- 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, 5.3)
- ACTEMRA doses exceeding 800 mg per infusion are not recommended in RA patients. (2.1, 12.3)

Administration of Intravenous formulation (2.6)
- For adults, PJIA and SJIA patients at or above 30 kg, dilute to 100 mL in 0.9% or 0.45% Sodium Chloride for intravenous infusion using aseptic technique.
- For PJIA and SJIA patients less than 30 kg, dilute to 50 mL in 0.9% or 0.45% Sodium Chloride 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 (2.7)
- Follow the Instructions for Use for prefilled syringe

Dose Modifications (2.8)
- Recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

---------- DOSAGE FORMS AND STRENGTHS----------
Single-use vials of ACTEMRA (20 mg per mL) for intravenous administration:
- 80 mg per 4 mL (3)
- 200 mg per 10 mL (3)
- 400 mg per 20 mL (3)

Prefilled Syringe (PFS) for subcutaneous administration:
- A single use PFS providing 162 mg of ACTEMRA in 0.9mL (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)
- Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. (2.8, 5.3)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.5)
- Live vaccines – Avoid use with ACTEMRA. (5.8, 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)
- **Nursing Mothers:** Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: May/2017

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF SERIOUS INFECTIONS

*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 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.

1.4 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.

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 (IV) 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 (2.8), Warnings and Precautions (5.3), and Adverse Reactions (6.1)]*.
- Doses exceeding 800 mg per infusion are not recommended in RA patients *[see Clinical Pharmacology (12.3)]*.

Recommended Subcutaneous (SC) 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 thrombocytopen*ia [see Dosage and Administration (2.8), Warnings and Precautions (5.3), 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 (2.8)]*.
- Intravenous administration is not approved for GCA.

2.3 Polyarticular Juvenile Idiopathic Arthritis

ACTEMRA may be used alone or in combination with methotrexate. 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

- Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.
- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.8)]*.
- Subcutaneous administration is not approved for PJIA.

2.4 Systemic Juvenile Idiopathic Arthritis

ACTEMRA may be used alone or in combination with methotrexate. 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

- Do not change a dose based solely on a single visit body weight measurement, as weight may fluctuate.
- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.8)]*.
- Subcutaneous administration is not approved for SJIA.

2.5 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).

2.6 Preparation and Administration Instructions for Intravenous Infusion

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

- PJIA and SJIA patients **less than 30 kg**: use a **50 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride, and then follow steps 1 and 2 below.
- Adult RA, PJIA and SJIA 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, 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, 2.3, 2.4)]*.

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	0.2mL/kg
8 mg/kg	Adult RA SJIA and PJIA (≥30 kg of body weight)	0.4mL/kg
10 mg/kg	PJIA (< 30 kg of body weight)	0.5 mL/kg
12 mg/kg	SJIA (< 30 kg of body weight)	0.6mL/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 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 may be stored at 2° to 8°C (36° to 46°F) 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 may be stored at 2° to 8°C (36° to 46°F) 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.

2.7 Preparation and Administration Instructions for Subcutaneous Injection

ACTEMRA for subcutaneous injection is only approved for adult indications and is not indicated for the treatment of pediatric patients with PJIA or SJIA. ACTEMRA for subcutaneous injection is not intended for intravenous drip infusion.

- Assess suitability of patient for SC 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. 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) 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 appears to be damaged.

- Patients using ACTEMRA for subcutaneous administration should be instructed to inject the full amount in the syringe (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.

2.8 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 and Giant Cell Arteritis

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3)]:*	
Lab Value	**Recommendation**
Greater than 1 to 3x ULN	Dose modify concomitant DMARDs (RA) 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 (5.3)]:*	
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 (5.3)]:*	
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. 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

Single-use vials of ACTEMRA (20 mg per mL) for IV administration:

- 80 mg per 4 mL
- 200 mg per 10 mL

- 400 mg per 20 mL

Prefilled Syringe (PFS) for SC administration:
- A single-use prefilled glass syringe providing 162 mg of ACTEMRA in 0.9mL

4 CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA *[see Warnings and Precautions (5.5)]*.

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 (2.5), 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 Laboratory Parameters

Approved Adult Indications

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 (2.8)]*.

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 (2.8)]*.

Elevated Liver Enzymes

Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials *[see Adverse Reactions (6.1, 6.2)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

In one case, a patient who had received ACTEMRA 8 mg per kg monotherapy without elevations in transaminases experienced elevation in AST to above 10x ULN and elevation in ALT to above 16x ULN when MTX was initiated in combination with ACTEMRA. Transaminases normalized when both treatments were held, but elevations recurred when MTX and ACTEMRA were restarted at lower doses. Elevations resolved when MTX and ACTEMRA were discontinued.

- It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT or AST greater than 5x ULN treatment is not recommended.

– Monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, other liver function tests such as bilirubin should be considered. For recommended modifications based on transaminases *see [Dosage and Administration (2.8)]*.

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, then at approximately 24 week intervals.

– 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 infusion 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 (2.8)]*.

5.4 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.

5.5 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 (6.5)]*. 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)]*.

5.6 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.

5.7 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)]*.

5.8 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

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)]*.

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 (5.5)]*.

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 (5.3)]*.

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 (5.3)]*.

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 (2.6)]*. 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)]*.

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

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

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.

The data reflect the percentage of patients whose test results were positive for antibodies to tocilizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to tocilizumab with the incidence of antibodies to other products may be misleading.

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 (5.4)]*.

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 (SC) and 8 mg/kg intravenously (IV) 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 SC or placebo in 656 patients. All patients in both studies received background non-biologic DMARDs.

The safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions, 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 injection site reactions 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 injection site reactions was 7.1% (31/437) and 4.1% (9/218) for the every other week SC ACTEMRA and placebo groups, respectively. These injection site reactions (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 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 6.5)*].

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 6.5)]*.

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%).

6.5 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 (5.5)]*.

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 x 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.

6.6 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of intravenous 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 (5.5)]*
- Stevens-Johnson Syndrome

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 (5.8)]*.

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 (5.8)]*

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 ($Il6^{-/-}$ 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

Safety and effectiveness of ACTEMRA in pediatric patients with conditions other than PJIA or SJIA have not been established. Children under the age of two have not been studied. SC administration has not been studied in pediatric patients. Testing of a murine analogue of tocilizumab did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

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.

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 (5.7)]*.

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

ACTEMRA (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.

ACTEMRA is supplied as a sterile, preservative-free solution for intravenous (IV) infusion at a concentration of 20 mg per mL. ACTEMRA is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available for intravenous administration containing 80 mg per 4 mL, 200 mg per 10 mL, or 400 mg per 20 mL of ACTEMRA. Injectable solutions of ACTEMRA are formulated in an aqueous solution containing disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate (as a 15 mmol per L phosphate buffer), polysorbate 80 (0.5 mg per mL), and sucrose (50 mg per mL).

ACTEMRA solution for subcutaneous administration is supplied as a sterile, colorless to yellowish, preservative-free liquid solution of approximately pH 6.0. It is supplied in a 1 mL ready-to-use, single-use prefilled syringe (PFS) with a needle safety device. Each device delivers 0.9 mL (162 mg) of ACTEMRA, in a histidine buffered solution composed of ACTEMRA (180 mg/mL), polysorbate 80, L-histidine and L-histidine monohydrochloride, L-arginine and L-arginine hydrochloride, L-methionine, and water for injection.

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 IV doses or the 162 mg weekly and every other weekly SC 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 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, 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 (5.3)]*.

12.3 Pharmacokinetics

Rheumatoid Arthritis—Intravenous Administration

The pharmacokinetics characterized in healthy subjects and RA patients suggested that PK is similar between the two populations. The clearance (CL) of tocilizumab decreased with increased doses. At the 10 mg per kg single dose in RA patients, mean CL was 0.29 ± 0.10 mL per hr per kg and mean apparent terminal $t_{1/2}$ was 151 ± 59 hours (6.3 days).

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis of 1793 rheumatoid arthritis patients treated with ACTEMRA 4 and 8 mg per kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{min}) was observed for doses of 4 and 8 mg per kg every 4 weeks. Maximum concentration (C_{max}) increased dose-proportionally. At steady-state, estimated

AUC and C_{min} were 2.7 and 6.5-fold higher at 8 mg per kg as compared to 4 mg per kg, respectively. In a long-term study with dosing for 104 weeks, observed C_{min} was sustained over time.

For doses of ACTEMRA 4 mg per kg given every 4 weeks, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800 mcg•h per mL, 1.49 ± 2.13 mcg per mL, and 88.3 ± 41.4 mcg per mL, respectively. The accumulation ratios for AUC and C_{max} were 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{min} (1.96). Steady-state was reached following the first administration for C_{max} and AUC, respectively, and after 16 weeks C_{min}. For doses of ACTEMRA 8 mg per kg given every 4 weeks, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 mcg•h per mL, 9.74 ± 10.5 mcg per mL, and 183 ± 85.6 mcg per mL, respectively. The accumulation ratios for AUC and C_{max} were 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35). Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight at or above 100 kg, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 mcg•h per mL, 19.0 ± 12.0 mcg per mL, and 269 ± 57 mcg per mL, respectively, which are higher than mean exposure values for the patient population. Therefore, ACTEMRA doses exceeding 800 mg per infusion are not recommended *[see Dosage and Administration (2.1)]*.

Rheumatoid Arthritis—Subcutaneous Administration

The pharmacokinetics of tocilizumab was characterized using a population pharmacokinetic analysis using a database composed of 1759 rheumatoid arthritis patients treated with 162 mg SC every week, 162 mg SC every other week, and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. For the 162 mg every week dose, the estimated mean (±SD) steady-state AUC_{1week}, C_{min} and C_{max} of tocilizumab were 8200 ± 3600 mcg•h/mL, 44.6 ± 20.6 mcg/mL, and 50.9 ± 21.8 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.83, 6.37, and 5.47, respectively. Steady state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the 162 mg every other week dose, the estimated mean (±SD) steady-state AUC_{2week}, C_{min}, and C_{max} of tocilizumab were 3200 ± 2700 mcg•h/mL, 5.6 ± 7.0 mcg/mL, and 12.3 ± 8.7 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 5.6, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

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 SC every week or with 162 mg SC every other week.

For the 162 mg every week dose, the estimated mean (±SD) steady-state Cavg, Cmin and Cmax of tocilizumab were 71.3 ± 30.1 mcg/mL, 68.1± 29.5 mcg/mL, and 73 ± 30.4 mcg/mL, respectively. The accumulation ratios for Cavg or AUCtau, Cmin, and Cmax 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 mean (±SD) steady-state Cavg, Cmin, and Cmax of tocilizumab were 16.2 ± 11.8 mcg/mL, 11.1 ± 10.3 mcg/mL, and 19.3 ± 12.8 mcg/mL, respectively. The accumulation ratios for Cavg or AUCtau, Cmin, and Cmax were 2.8, 5.6, and 2.3 respectively. Steady-state was reached after 14 weeks.

Polyarticular Juvenile Idiopathic Arthritis—Intravenous Administration

The pharmacokinetics of tocilizumab was determined using a population pharmacokinetic analysis on a database composed of 188 patients with polyarticular juvenile idiopathic arthritis.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 4 weeks, the estimated mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 29500 ± 8660 mcg•hr/mL, 182 ± 37 mcg/mL and 7.49 ± 8.2 mcg/mL, respectively.

For doses of 10 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 4 weeks, the estimated mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 23200 ± 6100 mcg•hr/mL, 175 ± 32 mcg/mL and 2.35 ± 3.59 mcg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{min} for 10 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) doses, respectively. No accumulation for C_{max} was observed.

Systemic Juvenile Idiopathic Arthritis—Intravenous Administration

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with SJIA treated with 8 mg per kg (patients with a body weight at or above 30 kg) or 12 mg per kg (patients with a body weight less than 30 kg), given every 2 weeks. The estimated mean (± SD) $AUC_{2\ weeks}$, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 mcg•hr per mL, 245 ± 57.2 mcg per mL and 57.5 ± 23.3 mcg per mL, respectively. The accumulation ratio for C_{min} (week 12 over week 2) was 3.2 ± 1.3. Steady state was reached on or after week 12. Mean estimated tocilizumab exposure parameters were similar between the two dose groups defined by body weight.

Absorption

Following SC dosing in RA and GCA patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 0.8.

In RA patients the median values of Tmax 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.

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 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 0.94 L, the peripheral volume of distribution was 1.60 L resulting in a volume of distribution at steady state of 2.54 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, 5.8 mL per h in pediatric patients with PJIA, and 7.1 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 IV 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 SC 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 SC every week dosing regimen and between 4.2 and 7.9 days for 162 mg SC every other week dosing regimen.

The $t_{1/2}$ of tocilizumab in children with PJIA is up to 16 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.

The $t_{1/2}$ of tocilizumab in pediatric patients with SJIA is up to 23 days for the two body weight categories at week 12.

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 SC 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 Cavg 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 Cavg 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 and GCA 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 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 was a 104-week study with an ongoing 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 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 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 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

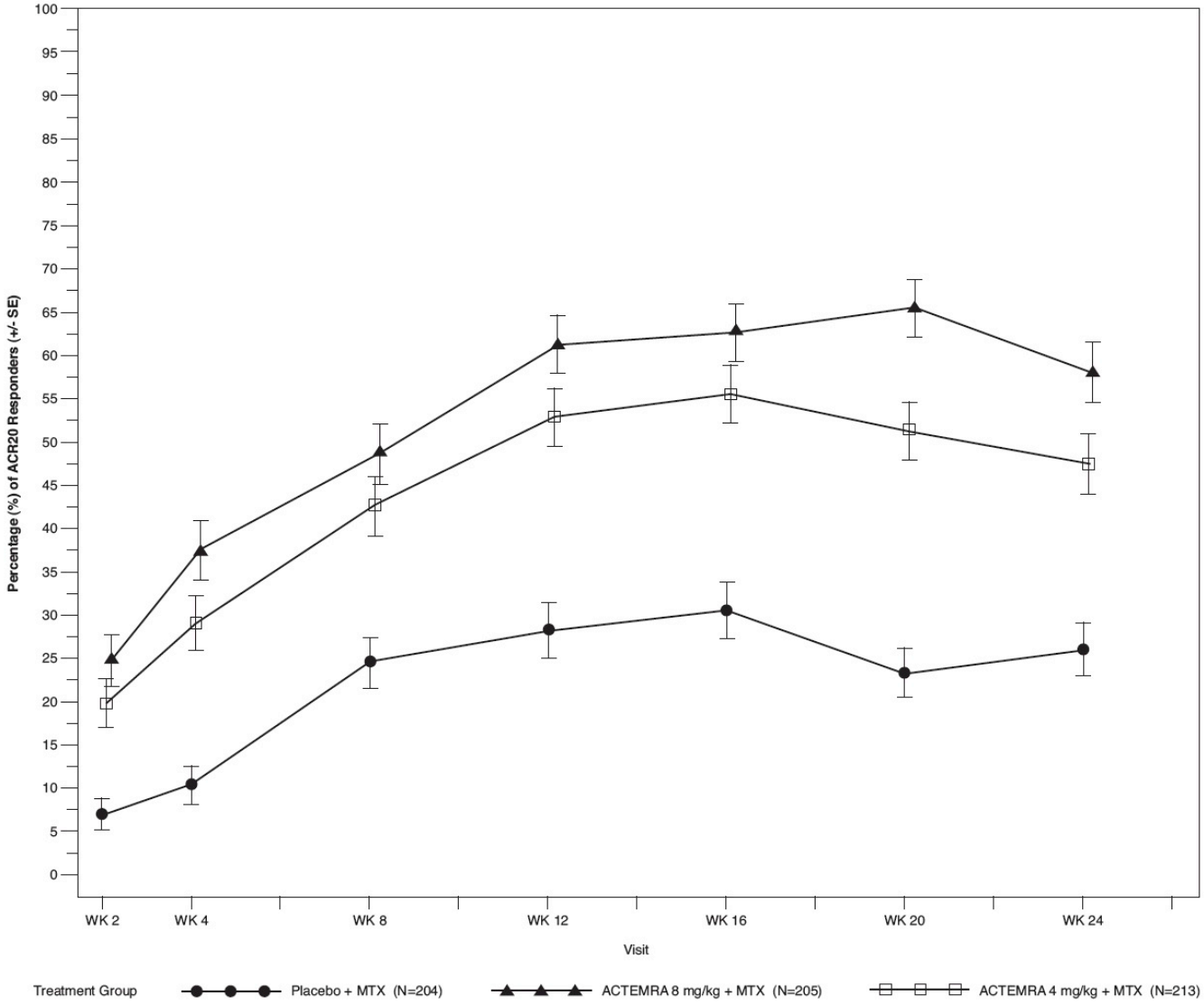
[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

[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 $\leq$ 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 $\geq$ 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.

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) was a non-inferiority study that compared the efficacy and safety of ACTEMRA 162 mg administered every week subcutaneously (SC) to 8 mg per kg intravenously every four weeks. The second study (SC-II) was a placebo controlled superiority study that evaluated the safety and efficacy of ACTEMRA 162 mg administered every other week SC 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 ACTEMRA intravenous 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 SC 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 SC 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 SC every week, IV 8 mg/kg, SC 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, 251 screened patients with new-onset or relapsing GCA were randomized to one of four treatment arms. Two SC 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 $\geq$ 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 $\geq$ 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 Polyarticular Juvenile Idiopathic Arthritis-Intravenous Administration

The efficacy of ACTEMRA was assessed in a three-part study 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 IV 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 IV 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.

14.5 Systemic Juvenile Idiopathic Arthritis-Intravenous Administration

The efficacy of ACTEMRA for the treatment of active SJIA was assessed in 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 9**.

Table 9 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	91%	24%
Weighted difference[a]	67	-
(95% CI)[b]	(51, 83)	
JIA ACR 50		
Responders	85%	11%
Weighted difference[a]	74	-
(95% CI) [b]	(58, 90)	
JIA ACR 70		
Responders	71%	8%
Weighted difference[a]	63	-
(95% CI) [b]	(46, 80)	

[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.

16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ACTEMRA (tocilizumab) is supplied in single-use vials as a preservative-free, sterile concentrate (20 mg per mL) solution for intravenous infusion. The following packaging configurations are available:

Individually packaged, single-use vials:

NDC 50242-135-01 providing 80 mg per 4 mL

NDC 50242-136-01 providing 200 mg per 10 mL

NDC 50242-137-01 providing 400 mg per 20 mL

For Subcutaneous Injection
ACTEMRA (tocilizumab) for subcutaneous administration is supplied as a sterile preservative-free liquid solution in a single-use prefilled syringe. The following packaging configurations are available:

NDC 50242-138-01 prefilled syringe providing 162 mg per 0.9mL

Storage and Stability: Do not use beyond expiration date on the container, package or prefilled syringe. ACTEMRA must be refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect the vials and syringes from light by storage in the original package until time of use, and keep syringes dry. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patient Counseling

Advise patients and parents or guardians of minors with PJIA or SJIA of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

- **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 SC 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 from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes, 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 and syringes should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper syringe and needle 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)]*.

MEDICATION GUIDE

ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Solution for Intravenous Infusion

ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Injection, Solution for Subcutaneous Administration

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. **Changes in certain laboratory test results.** Your healthcare provider should do blood tests before you start receiving ACTEMRA. If you have rheumatoid arthritis (RA) or giant cell arteritis (GCA) your healthcare provider should do blood tests 4 to 8 weeks after you start receiving ACTEMRA 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 test 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, and then every 6 months after that.

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.

4. **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.
- Adults with giant cell arteritis (GCA).
- People with active PJIA ages 2 and above.
- People with active SJIA ages 2 and above.

ACTEMRA is not approved for subcutaneous use in people with PJIA or SJIA.
It is not known if ACTEMRA is safe and effective in children with PJIA or SJIA under 2 years of age or in children with conditions other than PJIA or SJIA.

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. have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if ACTEMRA will harm your unborn baby. **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.
- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take ACTEMRA or breast-feed. You should not do both.

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, or SJIA:

- 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.
- 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 or Giant Cell Arteritis:

- **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-use Prefilled Syringe.
- You may also receive ACTEMRA as 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.
- 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
  - o chest pain
  - o feeling dizzy or faint
  - o 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: sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate.

Inactive ingredients of Subcutaneous ACTEMRA: L-arginine, L-arginine hydrochloride, L-methionine, L-histidine, L-histidine hydrochloride monohydrate.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: May/2017

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/s/

BADRUL A CHOWDHURY
05/22/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s112

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
Division Director Summary

Date	*See electronic stamp date*
From	Nikolay P. Nikolov, M.D. Badrul A. Chowdhury, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review Division Director Summary Review
BLA # **Supplement#**	sBLA 125276/112 sBLA 125472/24
Applicant	Hoffman La Roche, Inc.
Date of Submission	Received November 22 and 23, 2016
PDUFA Goal Date	May 22 and 23, 2017
Proprietary Name / Established (USAN) names	Actemra (tocilizumab)
Dosage forms / Strength	A single use 1.0 mL Pre-Filled Syringe (PFS) providing 162 mg of ACTEMRA in 0.9mL (No new dosage forms or strengths were proposed)
Proposed Indication(s)	Treatment of adult patients with giant cell arteritis
Recommended:	*Approval, with revisions to proposed label*

1. Introduction

This memorandum reviews the regulatory background and the evidence supporting the efficacy and safety of this supplemental biologics license application (sBLA) submitted by Hoffman La Roche, Inc, for subcutaneous tocilizumab (Actemra) seeking licensure for a new indication, treatment of adult patients with giant cell arteritis (GCA).

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). It is an FDA-approved therapeutic biologic product that is available and marketed in the United States as an intravenous (IV) formulation (original BLA 125276, approved January 2010) and as a subcutaneous (SC) formulation (original BLA 125472, approved October 2013). Intravenous TCZ is approved for treatment of moderate to severely active rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (SJIA), and polyarticular juvenile idiopathic arthritis (PJIA). Subcutaneous TCZ is approved for moderate to severely active RA. TCZ is supplied in single use vials for IV injection containing 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL of TCZ. TCZ also is supplied in a 1.0 mL single-use prefilled syringe (PFS), with a needle safety device that delivers 0.9 mL (162 mg) of TCZ.

The present efficacy supplement is submitted in support of a new proposed indication for SC tocilizumab, treatment of adult patients with giant cell arteritis (GCA). GCA is a potentially organ- and life-threatening disorder characterized by medium to large-size vasculitis with systemic inflammation, and for which there are currently no approved treatments. Systemic corticosteroids are the mainstay of treatment in patients with suspected or confirmed disease, usually initiated at high doses and slowly tapered over months once the disease is controlled. Other immunosuppressives (such as methotrexate, cyclophosphamide, azathioprine, leflunomide, cyclosporine, and dapsone) have been used in an attempt to reduce or discontinue steroid use, with mixed results. A Breakthrough Therapy designation was granted for tocilizumab for GCA on August 31, 2016. Given the unmet need and the seriousness of the disease, this application was reviewed as a 6-month priority review.[1]

2. Background

Giant-cell arteritis (GCA) is a systemic inflammatory vasculitis that manifests almost in large-sized arteries, predominantly the extra-cranial branches of the carotid arteries. It occurs in the sixth to eighth decades. In the United States, GCA predominantly affects Caucasians of Scandinavian descent (in Olmsted County, Minnesota, the annual incidence is 17 cases per 100,000 people ≥ 50 years of age)[2] and is rare among African Americans. Two categories of GCA have been distinguished: 1) cranial GCA, predominantly affecting the branches of the cranial arteries and 2) large-vessel GCA (LV-GCA), involving the aorta and its primary branches. Cranial symptoms typically include persistent headache, scalp tenderness, and jaw claudication. Visual manifestations occur in approximately 30% of patients, with permanent visual loss affecting approximately 15% of patients. Patients with LV-GCA generally present with symptoms of vascular insufficiency, particularly arm claudication, and manifestations of systemic inflammation such as fatigue, general malaise, fever, anorexia, weight loss, and night sweats. LV-GCA tends to affect patients who are younger than those with cranial GCA, and cranial symptoms are often absent. GCA is diagnosed based on the American College of Rheumatology (ACR) clinical, laboratory, and histopathologic criteria for GCA (Table 1) that distinguishes it from other vasculitides.[3] A patient is classified with GCA if at least 3 of these 5 criteria from Table 1 are present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%. Histopathological examination of a superficial temporal artery biopsy has been the "gold standard" for cranial GCA diagnosis. Diagnosis of LV-GCA generally requires the use of imaging techniques such as computed tomography (CT), CT angiography, magnetic resonance imaging, magnetic resonance angiography, or ultrasound.

There are no currently approved therapies for treatment of GCA. Standard practice includes treatment with high dose oral corticosteroids, 40-60 mg daily, upon suspicion of the diagnosis

[1] Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
[2] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009 Oct 15;61(10):1454-61
[3] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122−8.

of GCA, even prior to biopsy of the temporal artery or other evaluations to confirm the diagnosis. In patients who present with signs of visual loss or history of amaurosis fugax, intravenous pulse methylprednisolone may be considered prior to the initiation of oral glucocorticoids. Once the disease is controlled based on resolution of symptoms and normalization of inflammatory markers, a slow corticosteroid taper can be initiated. Low dose aspirin may be considered, in the absence of contraindications to its use, to decrease the rate of visual loss and cerebrovascular accidents. Other immunosuppressives (such as methotrexate, cyclophosphamide, azathioprine, leflunomide, cyclosporine, and dapsone) have been used in an attempt to reduce or discontinue steroid use, with mixed results.

Table 1. Giant-Cell Arteritis: Clinical, Laboratory, and Histopathology

Criterion	Comment
Age at onset ≥ 50 years	Development of symptoms or findings beginning at age 50 or older
New headache	New onset of or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation that is unrelated to arteriosclerosis of cervical arteries
Elevated ESR	ESR ≥ 50 mm/hr (Westergren method)
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells
ESR: erythrocyte sedimentation rate	

The development of TCZ for the treatment of GCA was supported by clinical data and published case reports suggesting that IL-6 plays a role in the pathogenesis of GCA. Upregulation of IL-6 was seen in temporal artery biopsy samples from GCA patients[4] and elevations of plasma levels of IL-6 were seen in patients with untreated GCA.[5] IL-6 levels correlate with disease activity and responsiveness to corticosteroid therapy.[6]

The tocilizumab GCA development program was discussed with the Applicant in pre-submission communications, including a PIND meeting, held in January 2012 and a Special Protocol Assessment non-agreement letter issued on December 05, 2012. Based on the Agency's feedback, the Applicant incorporated blinding procedures using a dual assessor approach for laboratory and clinical evaluations. An additional placebo control arm where prednisone was tapered over 52 weeks was incorporated to better reflect the standard of care for GCA and to facilitate the comparisons of tocilizumab treatment to standard of care.

[4] Weyand CM, Hicok KC, Hunder GG, et al. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Ann Intern Med 1994; 121:484−91
[5] Dasgupta B and Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. Br J Rheumatol 1990;29:456−8.
[6] Weyand CM, Fulbright JW, Hunder GG, et al. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. Arthritis Rheum 2000;43:1041−8.

Comments on the Statistical Analysis Plan were provided in August 2015 and June 2016. A pre-sBLA meeting was held August 29, 2016 to discuss the format and content of the supplement, including supportive analyses of the components of the primary endpoint and justification for the proposed dosing regimen.

A Breakthrough Therapy designation for the treatment of GCA was granted on August 31, 2016.

The data in this submission were derived from a single randomized, multi-center, double-blind, placebo-controlled study (WA28119), to assess the efficacy and safety of tocilizumab in patients with GCA. The study included a 52-week blinded period (Part 1) to evaluate two dose regimens of TCZ 162 mg SC QW and 162 mg SC Q2W, each in combination with a 26-week prednisone tapering regimen for the treatment of GCA versus placebo SC QW with a 26 week prednisone taper regimen (PBO+26 wk), and placebo SC QW with a 52 week prednisone taper regimen (PBO+52 wk). This was followed by a 104-week open-label period (Part 2), for a total study duration of 156 weeks where patients in remission at Week 52 were followed up off treatment and patients who were not in remission at Week 52, received TCZ 162 mg QW. The study enrolled 251 patients with new-onset or relapsing GCA from76 centers in 14 countries. The key efficacy endpoints were the proportions of patients in sustained remission from Week 12 to Week 52 in the TCZ treatment groups as compared to the PBO+26 week prednisone taper group and PBO+52 week prednisone taper group. Sustained remission was defined by a patient attaining from Week 12 through Week 52: (1) an absence of GCA signs and symptoms, as assessed by investigator, (2) normalization of erythrocyte sedimentation rate (ESR) (to <30 mm/hr without an elevation to ≥ 30 mm/hr attributable to GCA), (3) normalization of C-reactive protein (CRP) (to < 1 mg/dL, with an absence of successive elevations to ≥ 1mg/dL), and (4) successful adherence to the prednisone taper defined by not more than 100 mg of excess prednisone from Week 12 through Week 52. There has been no regulatory precedent with using the proposed endpoint. While the endpoint is considered to have a reasonable face validity to capture a clinically meaningful treatment effect on the disease, it has some limitations as a composite endpoint where the treatment effect could potentially be driven only by tocilizumab's direct effect on acute phase reactants, ESR and CRP, i.e. two of the components (2 and 3) of the endpoint. This limitation was addressed by additional supportive analyses based on the individual components of the endpoint, conducted by the FDA Statistical review team. Additional supportive controlled data included the cumulative prednisone dose received in the study, providing additional evidence of clinical benefit of TCZ in GCA.

The safety data supporting this submission included data from Study WA28119. A total of 250 patients were treated for up to 1 year in Part 1 and at least 88 patients treated for more than one year in Part 2. In the context of the well-characterized safety profile of tocilizumab in RA, the data provided in the submission were adequate to evaluate the efficacy and safety of tocilizumab for this unmet medical need population.

3. CMC/Device

No new CMC/Device information was submitted and no new information was needed to support with this supplement. The PFS device used in the program was the already approved single use 1.0 mL PFS presentation providing 162 mg of ACTEMRA in 0.9mL.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was submitted and no new information was needed to support with this supplement.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Primary Reviewer: Manuela L. T. Grimstein, Ph.D.
Clinical Pharmacology Team Leaders: Anshu Marathe, Ph.D., Ping Ji, Ph.D.
The following is excerpted from Dr. Grimstein's review.

The clinical pharmacology program in support of the GCA indication included sparse PK sampling data from study WA28119. In addition, a population PK analysis in GCA was also submitted.

Clinical Pharmacology

In GCA, tocilizumab exhibited nonlinear PK with greater than dose proportional increase in exposure following QW dosing regimen compared to Q2W regimen. It is noteworthy that that approximately 50% higher exposure was observed in patients with GCA compared to adult patients with RA. Further, the steady-state exposure (Ctrough) for 162 mg SC QW dosing regimen was approximately six-fold higher compared to the steady-state exposure for 162 mg SC Q2W regimen (data not shown). The population PK analysis suggests that GCA disease is a significant covariate impacting the linear clearance which significantly contributes to the observed difference in exposure to that in RA. The linear clearance for GCA patients was estimated to be 24% lower compared to that for RA patients, after adjustment for the effect of body weight on linear clearance. The reason for this observed difference and the clinical significance are unknown. As discussed in the section on Safety below, the safety profile of tocilizumab in GCA remained consistent with that in RA with the exception of higher rates of infections and serious infections, which is likely related to the higher doses of concomitant corticosteroids and patient demographics rather than the differences in exposure.

The clinical pharmacology team concluded, and we agree, that based on the data in this submission, no adjustment of the starting dose is recommended for any intrinsic factors, unlike in RA where the recommended SC dosing regimen is weight-tiered.

Exposure-Response Evaluation and Dose Selection

The dose-selection assessment was based on information from Study WA28119 which evaluated two dose regimens of TCZ, 162 mg SC QW and 162 mg SC Q2W, each in combination with a 26-week prednisone tapering regimen for the treatment of GCA. Pharmacodynamic markers such as IL-6, sIL6-R, C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR) were also evaluated in the study. Following TCZ treatment, the levels of the mechanism-based marker sIL-6R increased with time and with increasing TCZ exposure and were comparable to the mean levels in RA patients at steady state (Week 24) who received the same dose regimens (data not shown). With TCZ treatment, the levels of PD markers of inflammation, CRP and ESR, decreased rapidly in both TCZ treatment groups (data not shown). These changes were not observed in patients receiving placebo. The changes in these inflammatory markers were similar between the two TCZ doses providing support that in addition to the proposed 162 mg SC QW dose, the TCZ 162 mg Q2W dose impacted systemic inflammatory markers to a similar degree.

As discussed in further detail in the section on Efficacy, the results from Study WA28119 demonstrated similar efficacy with either 162 mg SC QW or 162 mg SC Q2W with respect to primary efficacy endpoint of the proportion of patients achieving sustained remission at Week 52. However, there was a trend towards improved response with the QW regimen compared with Q2W regimen for the absence of signs and symptoms of GCA, and cumulative prednisone use. These trends were not of the magnitude of difference seen with exposures between the two doses. For safety, there were not consistent marked differences in the incidence of AEs between the two dosing regimens except for higher incidence of serious infections with the higher TCZ 162 mg SC QW dose, as detailed in the section on Safety in this document.

In summary, despite the six-fold higher exposures of the TCZ 162 mg SC QW dose compared to 162 mg SC Q2W dose, both TCZ dosing regimens showed similar efficacy compared to placebo. While there were trends towards improved response with the QW regimen compared with Q2W regimen, this was counterbalanced by a higher incidence of overall and serious infections in the QW regimen compared with Q2W regimen. Based on these contextual pieces, a consideration of both TCZ 162 mg SC QW dosing regimen and 162 mg SC Q2W dosing regimen is reasonable for labeling.

Immunogenicity

Overall, the incidence of treatment-emergent anti-drug antibodies in Study WA28119 was low (1.1% [n=1] for the QW regimen and 6.5% [n=3] for the Q2W regimen). Thus, given the small numbers, data are limited to draw definitive conclusions of the effect of immunogenicity on tocilizumab pharmacokinetics, efficacy, and safety.

Conclusion

The clinical pharmacology review team concluded, and we agree, that the information submitted was adequate to support approval of the sBLA from their perspective, provided that agreement can be reached regarding the language in the label. The team also concluded that the proposed dosing regimen of tocilizumab 162 mg SC QW appears reasonable and that the dosing regimen of 162 mg SC Q2W might be an option to some patients based on clinical considerations. We agree with these conclusions. The team proposed editorial changes to the clinical pharmacology section of labeling and we agree with these changes.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Rachel Glaser, M.D.
Primary Statistical Reviewer: William Koh, Ph.D.
Statistical Team Leader: Gregory Levin, Ph.D.

Overview of Study Design

Study WA28119 was a randomized, double-blind, multi-site, multiple arm, parallel-group, placebo-controlled study conducted to assess the efficacy and safety of tocilizumab (TCZ) in adult patients with new-onset and relapsing active GCA. The GCA classification criteria used in the study were adopted from the 1990 ACR classification criteria.[7] Active disease was defined based on the presence of cranial symptoms of GCA or symptoms of polymyalgia rheumatica, and temporal artery biopsy or protocol-defined imaging confirming the diagnosis of vasculitis. New-onset GCA was defined as GCA diagnosed within 6 weeks of the baseline visit and relapsing GCA was defined as GCA diagnosed >6 weeks before baseline and previous treatment with ≥40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at any time. Enrollment of relapsing patients was preferentially limited to 70% but could be increased based on rate of enrollment of new-onset versus relapsing.

A 52 week double blind treatment period (Part 1) was followed by a 104-week open-label period (Part 2). Following a screening period of up to 6 weeks, during which time patients could receive glucocorticoids for treatment of GCA at the discretion of the investigator, patients were randomized 1:1:2:1 by interactive voice/web-based response system to receive one of the following treatment regimens:

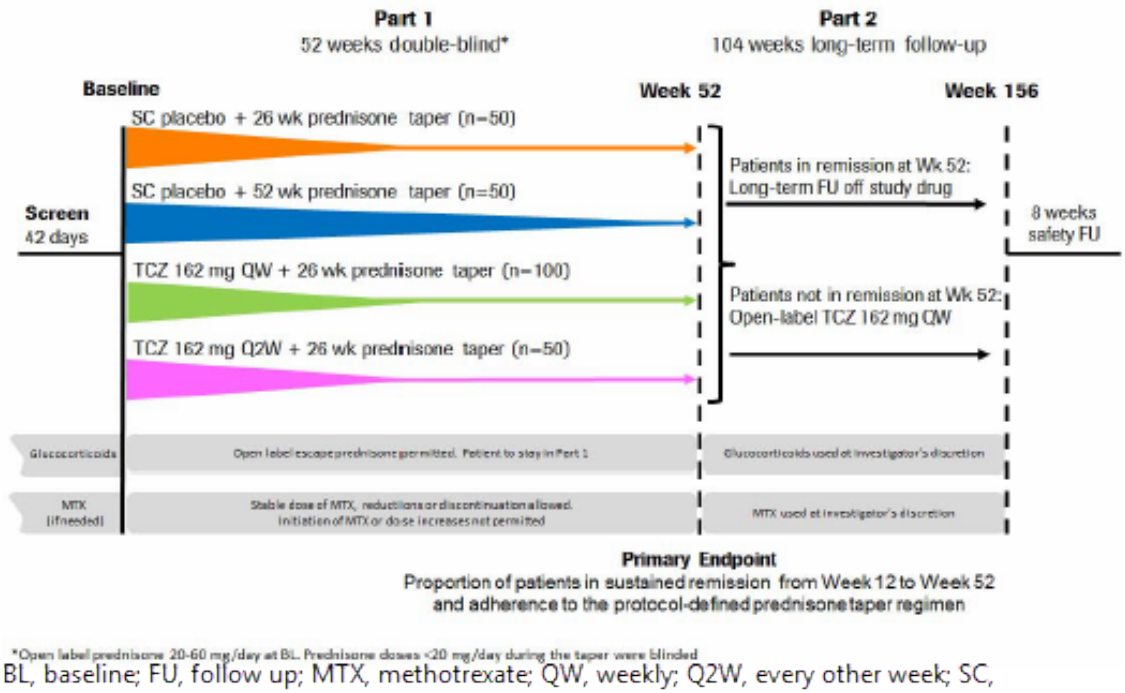
[7] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122−8.

- Placebo SC weekly (QW)+26-week prednisone taper regimen (PBO+26wk; n=50)
- Placebo SC QW+52-week prednisone taper regimen (PBO+52wk; n=50)
- 162 mg TCZ SC QW+26-week prednisone taper regimen (TCZ QW; n=100)
- 162 mg TCZ SC every other week (Q2W)+26-week prednisone taper regimen (TCZ Q2W; n=50)

Randomization was stratified by baseline prednisone dose (>30 mg/day and ≤30 mg/day). At the time of the baseline visit, the daily prednisone dose had to be within the range of 20-60 mg/day.

Key design features of Study WA28119 are summarized in Figure 1**Error! Reference source not found.**.

Figure 1. Study WA28119 Scheme



BL, baseline; FU, follow up; MTX, methotrexate; QW, weekly; Q2W, every other week; SC, subcutaneous; TCZ, tocilizumab.

Source: Clinical Study Report

Randomized patients were assessed weekly for signs and symptoms of the disease for the first four weeks of the study, and then every 4 weeks from Week 4 to Week 52. The evaluation of clinical signs and symptoms by the Clinical Assessor included the following:

- Fever (≥ 38°C or 100.4°F),
- Symptoms of PMR (morning stiffness and/or pain, in the shoulder and/or hip girdles),
- Localized headache, temporal artery or scalp tenderness,
- Visual signs or symptoms such as acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy (A-AION), transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes) ,

- Jaw or mouth pain,
- New or worsened extremity claudication,
- Other features judged by the Clinical Assessor to be consistent with a GCA or PMR flare.

Separate Clinical and Laboratory Assessors were used to maintain the blinding as TCZ is known to suppress levels of acute phase reactants which could potentially induce biases in the assessment of the primary endpoint.

Escape Therapy

During the open-label prednisone taper (patients on prednisone doses ≥20 mg/day), patients who experienced a disease flare or who were unable to adhere to the prednisone tapering schedule due to persistent disease activity, received open-label escape prednisone based on an investigator-defined regimen; these patients did not enter the double-blind taper phase (prednisone doses <20 mg/day). During the double-blind taper phase, patients who experienced a disease flare or who were unable to adhere to the prednisone tapering schedule, received open-label escape prednisone therapy at a dose of ≥20 mg/day and continued on an investigator-defined prednisone schedule. The patients who received escape therapy with prednisone continued to receive blinded TCZ or placebo injections and study assessments as per the schedule of assessments for the entire 52 weeks of Part 1. These patients could subsequently enter Part 2 of the study.

Study Conduct

Study WA28119 enrolled 251 patients with new-onset or relapsing GCA from76 centers in 14 countries. The majority of patients were Caucasian (96.8%), female (74.9%) with a mean age of 69 years, representative of the population of patients with GCA. Approximately 20% of the patients were enrolled at sites in the United States, and the remainder of the patients were enrolled in Europe (79.3%) and Canada (0.8%). Baseline demographics were generally balanced between treatment groups. Patients met criteria for GCA as defined in the inclusion criteria; approximately 78.5% of patients met ACR classification criteria for GCA.[8] All patients were 50 years of age or older and 96% of patients had a history of ESR ≥50 mm/hr, while 83% had a history of a CRP ≥2.45 mg/dL. New-onset localized headache (67.3%) was the most frequent cranial symptom of GCA, while 62.2% of patients reported symptoms of polymyalgia rheumatica (PMR). Approximately 10% of patients experienced ischemia-related visual loss prior to enrollment. The diagnosis of GCA was confirmed by temporal artery biopsy in 62.2% of the overall population, while imaging results were positive in 45.8% of the patients. There were small imbalances between groups with respect to baseline disease characteristics. For example, placebo + 26-week prednisone taper had on average longer disease duration (median 80 days) compared to for the rest of the groups (median 40 to 50 days). These differences however, are not unexpected given the study sample size and are unlikely to significantly affect the conduct and outcomes of the study. The overall study

[8] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122−8.

population is reflective and representative of the intended population of adults with GCA with active disease.

Patient Disposition

A high proportion of the randomized patients (84%) remained on their assigned double-blind treatment at the end of the double-blind period of the study, Week 52, with highest retention rate in the placebo arm with 52-week prednisone taper (90%) compared to TCZ QW or TCZ Q2W arms (80 to 82%). The most common reason for treatment discontinuation was adverse events with this highest incidence in the TCZ QW group, followed by participant withdrawal without explicit reasons. There were similar numbers of patients who discontinued treatment on the placebo with 26-week prednisone taper and TCZ Q2W dosing regimen arms for adverse events reasons. Specific reasons for patients who discontinued double-blind study treatment during the double-blind period are summarized in Table 2. The incidence and reasons for withdrawal are not unexpected for the patient population and treatments administered.

Table 2. Summary of Reasons for Discontinuation of Study Treatment (Part 1 in Study WA28119, ITT population)

	PBO QW + 26-week Prednisone Taper (N=50)	**PBO QW + 52-week Prednisone Taper (N=51)**	**TCZ QW + 26-week Prednisone Taper (N=100)**	**TCZ Q2W + 26-week Prednisone Taper (N=50)[a]**	**Total**
Total	**9**	**5**	**18**	**9[a]**	**41**
Safety	**3**	**0**	**9**	**3**	**15**
Adverse Event	*3*	*0*	*9*	*3*	*15*
Non-Safety	**6**	**5**	**9**	**7**	**27**
Lost to Follow-up	*0*	*0*	*0*	*0*	*0*
Non-compliance	*0*	*0*	*1[b]*	*0*	*1*
Lack of Efficacy	*1*	*2*	*1*	*3*	*7*
Withdrawal by subject	*2*	*1*	*5*	*2*	*10*
Physician decision	*3[c]*	*1[d]*	*1[e]*	*1[f]*	*6*
Protocol Violation	*0*	*1*	*0*	*0*	*1*
Other	*0*	*0*	*1[g]*	*0*	*1*

Source: Adapted from Dr. Koh's Statistical Review, Table 8
[a]: One patient who withdrew immediately after being randomized and did not start double-blind treatment were excluded
[b]: Reason: "Patient will not take any study medication anymore"
[c]: Reasons included schedule for hip surgery, due to AE; due to flare and ineffectiveness of therapy
[d]: Reason cited was due to elevated liver enzymes
[e]: Reason cited was lack of efficacy
[f]: Reason cited was flaring with anterior ischemic optic neuropathy
[g]: Reason cited was bilateral pneumonia
Abbreviations: PBO=placebo; QW=every week; Q2W=every other week; TCZ=tocilizumab

Efficacy Results

Sustained Remission

The primary endpoint, the proportion of patients achieving sustained remission from Week 12 through Week 52, is a composite endpoint defined by: (1) absence of flare following induction of remission by Week 12 and where flare is defined as the recurrence of signs or symptoms of GCA and/or ESR ≥30 mm/hr attributable to GCA, (2) normalization of CRP (<1 mg/dL), (3) successful prednisone tapering, and (4) remaining in the study through 52 weeks. Patients who received >100 mg of additional glucocorticoid dosing from Week 12 to Week 52 were considered as not adhering to the prednisone taper regimen.

The results from the primary and key secondary analyses are summarized in Table 3**Error! Reference source not found.**. Protocol-defined sustained remission from Week 12 through Week 52 was observed in 56 (56%; N=100) patients on the TCZ QW with 26-week prednisone taper arm, 26 (53.1%; N=49) patients in the TCZ Q2W with 26-week prednisone taper arm, 9 (18%; N=51) patients in the placebo with 52-week prednisone taper arm, and 7 (14%; N=50) patients in the placebo with 26-week prednisone taper arm. The primary objective compared TCZ QW and TCZ Q2W to the placebo arm with 26-week prednisone taper, and showed statistically significantly higher probabilities of sustained remission, with absolute increases versus placebo with 26-week taper of 42% (99.5% confidence interval or CI: 18% - 66%; p<0.0001) and 39% (99.5% CI: 12% - 66%; p<0.0001) respectively. The key secondary objective was to compare TCZ, to what the review team considers to be a reasonable representation of standard of care, placebo with 52-week prednisone taper; TCZ QW and TCZ Q2W both demonstrated higher probabilities of sustained remission, with absolute increases versus placebo with 52-week taper of 38% (99.5% CI: 14% - 62%; p<0.0001) and 35% (99.5% CI: 9% - 62%; p=0.0002), respectively.

Sensitivity analyses were conducted to evaluate the treatment effect on the individual components of sustained remission. Findings remained consistent for individual components 2 and 3 for both doses, as compared to both placebo arms. Evidence for TCZ QW based on one of the key component s of the primary endpoint, absence of signs and symptoms of GCA, remained compelling and robust against both placebo arms. Results based on this component comparing TCZ Q2W to both placebo arms were less compelling, and there was a suggestion of greater improvement for this endpoint on QW than Q2W dosing.

Table 3. Primary, Key Secondary, and Sensitivity Analyses Comparing the Two Tocilizumab (TCZ) Dosing Regimens with the Placebo (PBO) with 26-week Prednisone Taper and PBO with 52-week Prednisone Taper Arms

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Protocol-defined sustained remission	7 (14%)	9 (18%)	56 (56%)	26 (53%)
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			42% (18%, 66%)	39% (12%, 66%)
p-value			<0.0001	<0.0001
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			38% (14%, 62%)	35% (9%, 62%)
p-value			<0.0001	0.0002
Individual components of sustained remission				
Absence of signs and symptoms of GCA[a]	20 (40%)	23 (45%)	69 (69%)	28 (57%)[a]
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			29% (5%, 53%)	17% (-11%, 45%)
p-value			0.0007	0.0968
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			24% (0.3%, 47%)	12% (-16%, 40%)
p-value			0.0046	0.2344
Absence of elevated ESR attributable to GCA[a]	20 (40%)	22 (43%)	83 (83%)	37 (76%)[a]
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			43% (20%, 66%)	36% (8%, 63%)
p-value			<0.0001	0.00045
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			40% (18%, 62%)	32% (5%, 60%)
p-value			<0.0001	0.0010
Normalization of CRP[a]	17 (34%)	13 (25%)	72 (72%)	34 (69%)[a]
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			38% (14%, 62%)	35% (7%, 64%)
p-value			<0.0001	0.0005
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			47% (23%, 70%)	44% (16%, 72%)
p-value			<0.0001	<0.0001
Successful prednisone tapering	10 (20%)	20 (39%)	60 (60%)	28 (57%)
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			40% (16%, 64%)	37% (10%, 65%)
p-value			<0.0001	0.0002
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			21% (-3%, 45%)	18% (-10%, 46%)
p-value			0.0160	0.0742

Source: Adapted from Dr. Koh's Statistical Review and analyses, Table 10

[a]: Reviewer results differ from the Applicant's IR response due to (1) P-values computed by the Applicant did not stratify by baseline prednisone category; (2) Reviewer accounted for an additional subject lost to follow-up who should have been considered a non-responder in Applicant analyses

Abbreviations: CI=confidence intervals; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; QW=every week; Q2W=every other week.

Effects on Concomitant Prednisone Use

Limiting long-term use, and potentially inherent toxicities, of systemic corticosteroids, is an important goal in the management of GCA. Thus, cumulative prednisone use over the course of the study was prospectively captured and analyzed. A summary of these analyses is presented in Table 4. There were numerical trends suggesting that the overall cumulative prednisone dose for the TCZ QW and Q2W doses was substantially lower than that in both of the placebo arms. Patients on TCZ Q2W averaged slightly higher overall prednisone dose use than patients on TCZ QW.

Table 4. Summary of Cumulative Prednisone Use to Week 52

	PBO QW + 26-week Prednisone Taper (N=50)	**PBO QW + 52-week Prednisone Taper (N=51)**	**TCZ QW + 26-week Prednisone Taper (N=100)**	**TCZ Q2W + 26-week Prednisone Taper (N=49)**
Mean (SD), mg	4049 (2084.8)	4469 (2205.7)	2327 (1303.1)	2618 (1818.4)
Geometric Mean, mg	3524	4022	2028	2199
Median, mg	3804	3902	1887	2207
Minimum – Maximum, mg	935 – 10174	2166.4 – 10704.8	812.6 – 6607.0	949.4 – 9838.4
Vs PBO with 26-week Ratio of geometric means 99% CI			0.57 (0.467 - 0.699)	0.61 (0.477 - 0.769)
Vs PBO with 52-week Ratio of geometric means 99% CI			0.50 (0.428 - 0.591)	0.53 (0.434 - 0.656)

Source: Adapted from Dr. Koh's Statistical Review, Table 17

Other Secondary Endpoints

Other secondary endpoints appeared consistent with the primary and key secondary objectives. For example, numerical trends of improvement were observed in patient-reported outcomes, such as SF-36 mental summary component, SF-36 physical summary component, and patient global visual analogue scale (VAS) assessment, for the dosing regimens of TCZ (either QW or Q2W) relative to both placebo with 26-week prednisone taper and placebo with 52-week taper at Week 52. This evidence is considered supportive at best given that these endpoints are not disease-specific and their relevance in assessing clinical benefit in GCA is unclear.

Subgroup analyses, based on sustained remission at Week 52 by age groups, gender, race, weight groups, geographic regions, or relapsing GCA status, showed numerical trends consistent with the primary findings. Interpretations within the subgroups were limited due to the much smaller number of subjects as well as the multiplicity introduced.

Summary

In summary, the FDA Statistical review team concluded, and we agree, that there was convincing evidence among patients with GCA from this single pivotal study that TCZ QW when used in conjunction with an appropriate prednisone taper is efficacious based on not only the protocol-defined sustained remission composite endpoint from Week 12 through Week 52,

but also based on the absence of signs and symptoms of GCA from Week 12 through Week 52. In addition, analyses based on signs and symptoms alone suggested a higher response probability on the QW than the Q2W dosing. Evidence from TCZ Q2W for the key supportive signs and symptoms endpoint was less convincing, and supportive results of total prednisone use indicate that additional prednisone (e.g., a slower tapering schedule) may be warranted for this dosing regimen.

- **Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed.**

Both the clinical and statistical review teams are in agreement, and we concur, that there is adequate and substantial evidence of efficacy for tocilizumab in GCA.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

The clinical and statistical review teams have identified several issues, listed below, that were important in evaluating the efficacy of tocilizumab and the reliability of the Applicant's data. However, all of these issues were addressed and resolved during the review of the submission:

- Comparison with under treated control (placebo with 26-week prednisone taper): the focus was on the superiority evaluation against placebo with 52-week prednisone taper, as an appropriate current standard of care comparator.
- Limitations of composite endpoint: The proposed primary efficacy endpoint of sustained remission at Week 52 following induction of remission at Week 12 is a composite endpoint. To ensure that the overall treatment effect was not driven by only the tocilizumab's known effects on the inflammatory biomarkers CRP and ESR without tocilizumab having any effect on the direct signs and symptoms of the patient's disease, the FDA statistical review team conducted additional supportive analyses based on the individual components of the endpoint. Of these individual component analyses, the most reliable and direct measure of how patients function and feel was considered the absence of signs and symptoms of GCA alone. In this analysis, the comparison of TCZ QW relative to the placebo arm with an appropriate taper demonstrated compelling (estimate 24%; 99.5% CI 0.3% to 46%) evidence of improvements in patient symptoms. The efficacy for TCZ Q2W was less compelling but demonstrated numerical improvements (estimate 12%; 99.5% CI 16% lower to 40% higher) in patient symptoms of GCA relative to the placebo arm with 52-week taper. There were trends toward a dose response, i.e., greater improvement on TCZ QW than Q2W in analyses of absence of signs and symptoms of GCA alone.
- Missing data: Even though the overall drop out was low (approximately 14% of the subjects were not followed through Week 52), there were differentially higher discontinuation rates related to adverse events on the TCZ arms relative to the placebo arms. However, tipping point sensitivity analyses provided reassurance of the robustness of the Applicant's results to violations in assumptions about the missing data.

- Total steroid use: It was challenging to reliably estimate the amount of steroids used after discontinuation because there are differences in clinical practice in steroid tapering, as well as the possibility that patients who drop out may be systematically different than patients who remain in the study. Despite these limitations, in additional analyses of total prednisone use standardized to follow-up in the study, both TCZ QW and TCZ Q2W showed considerably lower total prednisone use relative to the placebo arms, providing additional supportive evidence of benefit.
- Time to first flare following GCA remission: This analysis conditions on a post-randomization variable (whether a patient achieved remission), such that differences between the arms (or lack thereof) could be due to treatment effects or could be due to differences in the patient characteristics of the subsets who achieved remission on the different arms. The analysis does not preserve the integrity of randomization (b) (4)
- Single study providing the evidence of efficacy: The FDA Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* indicates situations in which a single study of a new treatment may be combined with independent substantiation from related, supportive study data to provide evidence of effectiveness. The Applicant chose to control the overall Type 1 error rate at the 2-sided level of 1%, adjusted for multiplicity by further testing the primary endpoint for each dose at 2-sided level of 0.005; this significance level is more stringent than the typical two-sided 5% level. Furthermore, the analysis of the primary endpoint of sustained remission comparing the TCZ QW arm placebo with 52-week taper demonstrated a large and highly statistically significant effect (estimated difference: 38%; $p<0.0001$). Results were shown to be robust to alternative missing data assumptions in sensitivity analyses investigating plausible scenarios, and further showed benefit in analyses of each of the individual components of this composite endpoint.
- Dose selection: This study investigated QW and Q2W dosing of TCZ with a 26-week prednisone taper and showed compelling results based on the protocol-defined primary endpoint for both doses. In the critical supportive analysis based on signs and symptoms of GCA alone, results remained statistically significant for the higher QW dose but not for the Q2W dose although there remained numerical trends toward benefit for the lower TCZ dose.

8. Safety

Primary Clinical Reviewer: Rachel Glaser, M.D.

- **Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing**

The safety profile of tocilizumab has been well-characterized in patients with RA, PJIA, and SJIA.[9] On that foundation, the Applicant has provided additional safety data for 150 patients with GCA treated with one of two TCZ dosing regimens during the double-blind treatment for 52 weeks in Part 1, and 88 patients treated in the ongoing long term extension with at least 100 weeks of total follow-up in Study WA28119. In this context, this is considered an adequate safety database to provide a reasonable assessment of safety of tocilizumab for this unmet medical need population.

Overall, these data remain consistent with safety data previously submitted for tocilizumab, and no new safety signals have been identified. The major risk of TCZ is serious infections, consistent with its potent immunosuppressive effects which appear to be numerically higher in GCA which is not unexpected for this patient population and high doses of concomitant systemic corticosteroids. TCZ manifested effects on laboratory parameters, such as decreased white blood cell count, increases in lipids, and liver enzyme elevation, although these lacked significant association with clinical adverse events. The data in this submission do not warrant a risk evaluation and mitigation and strategy (REMS).

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

There were no deaths reported during Part 1 of the study. There was one fatal event of aortic dissection reported in Part 2 as of the cutoff date of April 11, 2016. The aortic dissection occurred in a 62 year old female with a history of hypertension and relapsing GCA, previously treated with methotrexate and cyclophosphamide, who was randomized to the PBO+26 week group in Part 1. Aortic dissection is a recognized consequence of large vessel GCA and this event is most likely related to her underlying GCA.

Serious Adverse Events

A summary of non-fatal serious adverse events (SAEs) is presented in Table 5. During the 52-week controlled period of Study WA28119, a greater proportion of patients in the placebo treatment groups reported SAEs as compared with both TCZ groups. The most frequently reported SAEs were in the Infections and Infestations SOC. Treatment with corticosteroids is

[9] FDA-approved labeling for Actemra

associated with an increased risk of infections and the patients in the PBO treatment groups received higher doses of steroids than those in the TCZ treatment groups. Treatment with TCZ is also associated with an increased risk of serious infections and no numerical imbalances were observed to suggest an increase in the risk of infections with TCZ above that associated with steroid use in patients with GCA. A greater proportion of patients had infectious SAEs in the TCZ QW treatment group as compared to the TCZ Q2W group, based on the small numbers of patients.

Table 5. Patients with ≥1 SAEs by SOC and PT, Reported by ≥1 Patient in Any Treatment Group in Part 1 (Safety Population)

System organ class, n (%)	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Patients with ≥ 1 SAE	11 (22.0)	13 (25.5)	15 (15.0)	7 (14.3)
Total # of SAEs	15	21	27	10
Infections And Infestations	2 (4.0)	6 (11.8)	7 (7.0)	2 (4.1)
Vascular Disorders	2 (4.0)	1 (2.0)	4 (4.0)	2 (4.1)
Respiratory, Thoracic And Mediastinal Disorders	2 (4.0)	2 (3.9)	2 (2.0)	1 (2.0)
Cardiac Disorders	0	2 (3.9)	2 (2.0)	0
Injury, Poisoning and Procedural Complications	1 (2.0)	0	3 (3.0)	1 (2.0)
Nervous System Disorders	2 (4.0)	1 (2.0)	1 (1.0)	1 (2.0)
Gastrointestinal Disorders	2 (4.0)	0	1 (1.0)	0
Musculoskeletal And Connective Tissue Disorders	1 (2.0)	2 (3.9)	1 (1.0)	0
Eye Disorders	1 (2.0)	1 (2.0)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (2.0)	1 (2.0)	0	1 (2.0)
Immune System Disorders	0	0	1 (1.0)	1 (2.0)
Metabolism And Nutrition Disorders	0	1 (2.0)	0	1 (2.0)

Source: Adapted from Dr. Glaser's Clinical Review, Table 17
*Other includes single patients with SAEs of Cholangitis Infective, Chronic Sinusitis, Erysipelas, Genital Herpes Zoster, Pneumonia Haemophilus, Pyelonephritis, Respiratory Tract Infection, Urinary Tract Infection, Urosepsis, Deep vein thrombosis, Dry gangrene, Hypertension, Asthma, Dyspnoea, Dyspnoea exertional, nasal inflammation, Oropharyngeal pain, Pleural effusion, Pulmonary Embolism, Aortic Valve Stenosis, Cardiac failure, Cardiac failure chronic, Supraventricular tachycardia, Tachyarryhthmia, alcohol poisoning, laceration, meniscus injury, postoperative wound complication, tendon rupture, headache, paraesthesia, syncope, thrombotic stroke, transient ischaemic attack, diarrhea, stomatitis, arthralgia, fibromyalgia, osteoarthritis, tendon pain, glaucoma, breast cancer, malignant melanoma, ovarian adenoma, drug hypersensitivity, hypersensitivity, anxiety, stress, hepatic enzyme increased, and renal impairment

Discontinuations Due to Adverse Events

As indicated in Table 2, in the section on Patient Disposition, a greater proportion of patients in the TCZ QW and TCZ Q2W groups reported AEs leading to withdrawal from treatment (11.0% and 10.2%, respectively), as compared to the PBO+26 wk prednisone taper group (6.0%) and PBO+52 wk prednisone taper group (0%). Consistent with the tocilizumab safety profile, the greatest proportion of patients discontinued treatment due to AEs within the Infections and Infestations SOC.

Adverse Events of Special Interest

Adverse events of special interest (AESI) included but were not limited to, infections, opportunistic infections, malignancies, hepatic events, hypersensitivity, ISRs, stroke, myocardial infarction, anaphylactic reactions, GI perforations, bleeding events, and demyelinating events.

The proportions of patients with adverse events of special interest are summarized in Table 6. There were no reports of serious hepatic events, serious myocardial infarction events, serious gastrointestinal perforation events, serious bleeding events, or serious demyelinating AEs during the double-blind portion of the study up to Week 52.

Table 6. Adverse Events of Special Interest in Part 1 (Safety Population)

AESI, n (%)	**PBO QW + 26-week Prednisone Taper (N=50)**	**PBO QW + 52-week Prednisone Taper (N=51)**	**TCZ QW + 26-week Prednisone Taper (N=100)**	**TCZ Q2W + 26-week Prednisone Taper (N=49)**
Infections	38 (76.0)	33 (64.7)	75 (75.0)	36 (73.5)
Serious infections	2 (4.0)	6 (11.8)	7 (7.0)	2 (4.1)
Opportunistic infections	0	2 (3.9)	0	1 (2.0)
Malignancy	1 (2.0)	1 (2.0)	1 (1.0)	0
Serious Stroke	0	1 (2.0)	0	1 (2.0)
Hypersensitivity	1 (2.0)	1 (2.0)	1 (1.0)	2 (4.1)
Anaphylaxis (Sampson criteria)[10]	0	0	0	1 (2.0)
Injection site reactions	5 (10.0)	1 (2.0)	6 (6.0)	7 (14.3)
Source: Adapted from Dr. Glaser's Clinical Review, Table 20				

Infections
Infections/serious infections were the most common AESI. Opportunistic infections were also reported, including Herpes zoster (most commonly), cytomegalovirus infection, fungal and oropharyngeal candidiasis. The types of infections were consistent with those seen with tocilizumab and prednisone treatment and were balanced across the treatment groups.

Malignancy
Malignancies were reported in 3 patients during Part 1 of Study WA28119. One male patient in the PBO+26 wk prednisone taper group reported breast cancer and renal neoplasm, while one patient in the PBO+52 wk taper group group reported malignant melanoma and one patient in the TCZ QW group reported marginal zone lymphoma. In Part 2, there were 3 additional malignancies reported including invasive ductal breast carcinoma in 1 patient who received TCZ QW during Part 1, and basal cell skin cancer in 1 patient each in the TCZ QW and PBO+26 wk groups. None of the patients were receiving open-label TCZ in Part 2. The overall types of malignancy in GCA appear consistent with those in the general population and were balanced across the treatment groups.

[10] Sampson HA et al., *J Allergy Clin Immunol.* 2006 Feb;117(2):391-7

Laboratory abnormalities

Tocilizumab treatment has consistent and demonstrated effects on hepatobiliary, hematologic, and lipid laboratory parameters. These abnormalities have previously been described and explored in detail in the previous tocilizumab submissions. The data in this submission are consistent with previously described effects of tocilizumab on these laboratory parameters.

Immunogenicity

In study WA28119, all patients were tested at baseline and Week 8, Week 24, Week 36, and at completion of the double blind period at Week 52 for anti-TCZ antibodies (anti-drug antibodies, ADA). All samples were tested using a screening assay; positive tests were analyzed by a confirmation assay. If the confirmation assay was positive, a neutralizing assay to test ADA's neutralizing potential and an IgE assay to verify if the detected ADA were of the IgE isotype, were performed.

Overall, the incidence of treatment-emergent anti-drug antibodies was low (1.1% [n=1] for the QW regimen and 6.5% [n=3] for the Q2W regimen) in patients with GCA in study WA28119. These data were limited to draw definitive conclusions of the effect of immunogenicity on tocilizumab pharmacokinetics, efficacy and safety. However, this incidence of ADA formation is consistent with the low incidence seen with tocilizumab in other populations.[11] Further, ADAs were not observed in patients who experienced hypersensitivity or anaphylaxis.

Comparative Safety Profile

Overall, the safety profile of tocilizumab in GCA is consistent with that seen in adults with RA in terms of types of adverse reactions noted. Infections and infestations occurred most commonly, and TCZ-related laboratory abnormalities were also observed in GCA patients. GCA patients had higher rates of infections and serious infections than RA patients, however this is not unexpected given the severity of the underlying disease and use of other concomitant immunosuppressives, especially corticosteroids.

- **Discussion of primary reviewer's comments and conclusions**

Dr. Glaser has concluded, and we concur, that the types and rates of adverse events submitted with this supplement are generally consistent with those previously submitted for tocilizumab and has not identified any new safety signals. The safety profile of tocilizumab in GCA appears to be similar to the safety profile of tocilizumab in RA, with expected for the population higher overall infections and serious infections, and provides for an acceptable risk:benefit balance in this population. Further, Dr. Glaser concluded, and we concur, that a greater proportion of patients experienced serious infections in the TCZ QW compared to TCZ

[11] FDA-approved labeling for Actemra

Q2W treatment group which is a clinical consideration for the recommendation to also include TCZ Q2W as a dosing regimen in GCA.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

We concur that the safety profile, and risk:benefit balance, of Actemra for GCA is acceptable.

- **Discussion of notable safety issues (resolved or outstanding)**

Notable issues are described above.

9. Advisory Committee Meeting

No Advisory Committee meeting was convened for this efficacy supplement. No issues were identified warranting Advisory Committee input, as the efficacy of tocilizumab in the unmet medical need population was clear and substantial, with an acceptable safety profile that was consistent with the known safety profile of tocilizumab.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Thus, if TCZ is approved for the GCA indication, this approval would trigger PREA.

The new indication, GCA, is a disease that does not occur in pediatric population. On January 15, 2016 the FDA provided final agreement with the Applicant's initial Pediatric Study Plan (iPSP) to request a full waiver of the requirements to submit a pediatric assessment for GCA indication. Consistent with this agreement, in this application, the Applicant requested a full waiver from the requirements of a pediatric assessment. The TCZ pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting on April 19, 2017. PeRC agreed with the requested full waiver of the requirement to submit a pediatric assessment for GCA for TCZ. We agree with PeRC's recommendation. Thus, no post-marketing pediatric studies are required under PREA.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**—No issues.

- **Financial disclosures**—Acceptable.
- **Other GCP issues**—Not applicable.
- **OSI audits**—It was decided that Office of Scientific Investigations (OSI) inspection was not warranted in this case for the following reasons: 1) the product is already approved, 2) any specific individual site contained so few patients that it would be unlikely to affect overall results, and 3) the treatment effect size was very large, again suggesting that inspection of 2 or 3 clinical sites would not be likely to affect overall conclusions.
- **Other discipline consults**—None requested.
- **Any other outstanding regulatory issues—**None identified.

12. Labeling

- **Proprietary name**—No issues, already approved.
- **DMEPA and OPDP comments—**None.
- **Physician labeling**

  The primary proposed changes included:

  (1) the new indication of treatment of adult patients with giant cell arteritis (GCA),
  (2) dosing regimen for the SC route of administration for GCA patients,
  (3) clinical data in GCA patients for Section 6 Adverse Reactions, Section 12.3 Pharmacokinetics, and Section 14 Clinical Studies.

  The review team did not agree with the Applicant-proposed language on:

  (b) (4)

- **Carton and immediate container labels —** No issues.
- **Patient labeling/Medication guide** — The Medication Guide and patient labeling were revised to include reference to the GCA indication.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

We recommend approval of this efficacy supplement, provided agreement can be reached with the Applicant on revisions to the proposed label.

- **Risk Benefit Assessment**

The risk:benefit profile of tocilizumab in GCA is clearly favorable. The risks of tocilizumab treatment in this patient population appear to be qualitatively similar as those seen in adults with RA, with the primary serious risk being an increased risk of infection. Abnormalities in hepatobiliary, hematologic, and lipid parameters were also observed in GCA patients; however, as with RA, these abnormalities did not appear to be correlated with clinical adverse events. Although the risks of tocilizumab are not minimal, these are outweighed by the apparent benefits, which include induction and sustained remission of the disease, and reduction in the requirement for systemic corticosteroids.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)**

Tocilizumab was originally approved with a REMS in January 2010 consisting of a medication guide and communication plan. In August 2015, FDA determined that because the communication plan was no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS was no longer required for Actemra (tocilizumab) (refer to the letter posted under the approval history for US-licensed Actemra at Drugs@FDA with the action date August 18, 2015). No new safety signals were identified in this submission. Thus, no new REMS is warranted on the basis of the data in this submission.

- **Recommendation for other Postmarketing Requirements and Commitments**

None.

- **Recommended Comments to Applicant**

None.

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/s/

NIKOLAY P NIKOLOV
05/16/2017

BADRUL A CHOWDHURY
05/16/2017

Cross-Discipline Team Leader Review

Date	*See electronic stamp date*
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
BLA # **Supplement#**	sBLA 125276/112 sBLA 125472/24
Applicant	Hoffman La Roche, Inc.
Date of Submission	Received November 22 and 23, 2016
PDUFA Goal Date	May 22 and 23, 2017
Proprietary Name / Established (USAN) names	Actemra (tocilizumab)
Dosage forms / Strength	A single use 1.0 mL Pre-Filled Syringe (PFS) providing 162 mg of ACTEMRA in 0.9mL (No new dosage forms or strengths were proposed)
Proposed Indication(s)	Treatment of adult patients with giant cell arteritis
Recommended:	*Approval, with revisions to proposed label*

Hoffman La Roche, Inc submitted this efficacy supplemental biologics license application (sBLA) for subcutaneous tocilizumab (Actemra) seeking licensure for a new indication, treatment of adult patients with giant cell arteritis (GCA). The cross-discipline team leader (CDTL) review is complete and will be uploaded to DARRTS as a combined CDTL and Division Director Summary Review at the end of the review cycle. This reviewer recommends approval of this efficacy supplement for the following indication:

- Treatment of adult patients with giant cell arteritis

Refer to the combined CDTL and Division Director Summary Review for additional details.

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/s/

NIKOLAY P NIKOLOV
05/08/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s112

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125276/112; 125472/24
Priority or Standard	Priority
Submit Date(s)	November 22 and 23, 2016
Received Date(s)	November 22 and 23, 2016
PDUFA Goal Date	May 22 and 23, 2017
Division / Office	DPARP/OND
Reviewer Name(s)	Rachel L. Glaser, M.D.
Review Completion Date	April 28, 2017
Established Name	Tocilizumab
(Proposed) Trade Name	Actemra
Therapeutic Class	IL-6 inhibitor
Applicant	Hoffman-La Roche, Ltd
Formulation(s)	Intravenous (IV), Subcutaneous (SC)
Dosing Regimen	162 mg subcutaneously weekly and 162 mg subcutaneously every 2 weeks
Indication(s)	Giant Cell Arteritis (GCA)
Intended Population(s)	Adult patients with GCA

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of supplement 24 to Biologic Licensing Application (BLA) 125472 and supplement 112 to BLA 125276 to expand the indications of tocilizumab (TCZ) to include treatment of giant cell arteritis (GCA) in adult patients.

1.2 Risk Benefit Assessment

To support this submission, the Applicant conducted a single study, Study WA28119, a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in patients with GCA. Two hundred and fifty one patients with new-onset or relapsing GCA were randomized (1:1:2:1) to receive treatment with placebo subcutaneously (SC) weekly with a 26 week prednisone taper regimen (PBO+26 wk), placebo SC weekly with a 52 week prednisone taper regimen (PBO+52 wk), TCZ 162 mg SC weekly with a 26 week prednisone taper regimen (TCZ QW), or TCZ 162 mg SC every two weeks with a 26 week prednisone taper regimen (TCZ Q2W). The 52 week double blind period was followed by a 104 week open-label period. The primary and key secondary endpoints were the proportions of patients in sustained remission from Week 12 to Week 52 in the TCZ treatment groups as compared to the PBO+26 wk group (primary endpoint) and PBO+52 wk treatment group (key secondary endpoint). A significantly greater proportion of patients achieved a sustained remission at Week 52 in each of the TCZ dose groups as compared to both the PBO+26 wk and PBO+52 wk groups. Patients in the TCZ treatment groups had a decreased risk of first flares after remission and had lower median cumulative prednisone use as compared to the placebo groups. While the efficacy of the 2 TCZ dosing regimens was generally similar, trends towards improved response with the TCZ QW dose as compared with TCZ Q2W regimen were observed for sustained remission at Week 52, time to first flare after achieving remission, and cumulative prednisone use.

Safety and immunogenicity of the two dosing regimens were similar and consistent with the established safety profile for TCZ. The overall proportion of patients who experienced serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation were similar in the TCZ QW and TCZ Q2W groups. A greater proportion of patients experienced serious infections in the TCZ QW treatment group compared to TCZ Q2W group, but similar proportions of patients experienced serious infections in the TCZ QW and the PBO+52 wk groupsThe proportions of patients with infections overall were similar across the placebo and TCZ treatment groups. Common AEs were reported in similar proportions of patients in each treatment group. Rates of immunogenicity were low and not associated with changes in efficacy, pharmacokinetics (PK), or occurrence of safety events. Overall, treatment with TCZ

QW does not appear to pose an excessive additional risk for AEs as compared to treatment with TCZ Q2W in patients with GCA.

The approved dosing regimen for SC TCZ in rheumatoid arthritis (RA) is based on body weight. In WA28119, the observed TCZ exposure based on C_{trough} was 50% greater in the GCA population as compared to patients with RA, and an increase in exposure was further observed in GCA patients of lower body weight. While analysis by body weight groups is limited due to small numbers of patients in the low and, in particular, the high body weight subgroups, the proportions of patients in sustained remission at Week 52 in the lowest body weight group was numerically higher in the TCZ QW group as compared to the TCZ Q2W group, suggesting that at least some of these patients may still benefit from the higher exposure provided by the more frequent dosing regimen.

Both the TCZ QW and TCZ Q2W dosing regimens demonstrated overall similar improvement on the primary, key secondary, and secondary endpoints over the placebo treatment groups with similar safety profiles. The observed differences between the two TCZ dosing regimens are small, however there is a trend towards improved response with the TCZ QW dose regimen in sustained remission at Week 52, time to first flare after remission, and median cumulative prednisone use. Given the need for aggressive treatment of GCA to prevent serious acute and long-term sequelae, and the similar safety profiles of the two regimens, I agree with the Applicant-proposed dose of TCZ 162 mg SC QW. However, given the similar efficacy results, the TCZ Q2W dosing regimen may be preferable for some patients based on clinical considerations. Therefore, I recommend approval of both the weekly and every other week tocilizumab dosing regimens for treatment of giant cell arteritis. I note that TCZ is also approved as an intravenous (IV) formulation; however,studies using the IV dosing regimen(s) have not been submitted for regulatory review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Actemra was released from its REMS requirement (originally approved on January 8, 2010 and modified on October 21, 2013) on August 18, 2015. These supplements do not warrant new or modification of the previously released postmarketing risk evaluation and management strategies (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

TCZ is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1 subtype with a typical H_2L_2 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 IV and SC presentations. IV TCZ is supplied in single use vials containing 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL of TCZ in an aqueous solution of disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate, polysorbate 80, and sucrose. SC TCZ is supplied in a 1.0 mL single-use prefilled syringe, with a needle safety device, that delivers 0.9 mL (162 mg) of TCZ, in a histidine buffered solution of TCZ (180 mg/mL), polysorbate 80, L-histidine and L-histidine monohydrochloride, L-arginine and L-arginine hydrochloride, L-methionine, and water for injection.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently approved therapies for treatment of GCA. Standard practice includes treatment with high dose oral corticosteroids, 40-60 mg daily, upon suspicion of the diagnosis of GCA, even prior to biopsy of the temporal artery or other evaluations to confirm the diagnosis. In patients who present with signs of visual loss or history of amaurosis fugax, intravenous pulse methylprednisolone may be considered prior to the initiation of oral glucocorticoids (Dasgupta, 2010, Mukhtyar, 2009). Once the disease is controlled based on resolution of symptoms and normalization of inflammatory markers, a slow corticosteroid taper can be initiated. Low dose aspirin may be considered, in the absence of contraindications to its use, to decrease the rate of visual loss and cerebrovascular accidents (Dasgupta, 2010; Mukhtyar, 2009).

Methotrexate has been used off-label as adjunctive therapy in some patients. The conclusions from randomized controlled trials on its use have been mixed. A meta-analysis of 3 randomized controlled trials suggests a small decrease in cumulative steroid dose and higher probability of steroid discontinuation without relapse (Mahr, 2007). The 2010 British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines on the management of GCA recommend consideration of early introduction of methotrexate or alternative immunosuppressants as adjuvant therapy in the treatment of relapse (Dasgupta, 2010). Other agents described in case reports and case series to have potential beneficial effect in GCA treatment include cyclophosphamide, azathioprine, leflunomide,

cyclosporine, dapsone and tocilizumab. In a meta-analysis conducted to evaluate treatments for GCA, that included studies with different corticosteroid regimens, methotrexate, dapsone, infliximab, adalimumab, and hydroxychloroquine, no benefit was seen with adjunctive therapy (Yates, 2014), however the analysis was limited by the small number of studies using the various adjunctive agents.

2.3 Availability of Proposed Active Ingredient in the United States

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). IV TCZ is approved for treatment of moderate to severely active rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (SJIA), and polyarticular juvenile idiopathic arthritis (PJIA), and SC TCZ is approved for moderate to severely active RA. In India and Japan, IV TCZ is also approved for treatment of Castleman's disease.

2.4 Important Safety Issues With Consideration to Related Drugs

Study WA28119 was designed based on the well-characterized safety profile of tocilizumab in rheumatoid arthritis, SJIA, and PJIA. Potential risks observed with TCZ treatment, as well as those associated with immunomodulating biologic therapies, including infections, malignancies, gastrointestinal (GI) perforations, cardiovascular safety, and demyelinating events, were considered. Potential risks of a foreign protein were also considered and include administration or immune reactions, such as hypersensitivity, injection site reactions, and immunogenicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At a PIND meeting, held 17Jan2012, discussion centered on the following:

- Support for the proposed dosing and route of administration in GCA
- Inclusion of a corticosteroid (CS) treatment group to receive CS for a 12 month controlled period, consistent with standard of care treatment
- Requirement for normalization of erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) may bias results in favor of TCZ. Sensitivity analyses to be conducted on proportion of patients who fail to meet definition of remission on the basis of ESR and CRP alone
- Concern for unblinding of investigators with results of inflammatory markers
- Definition of refractory disease could include patients with suboptimal treatment

The Applicant subsequently submitted a Special Protocol Assessment (SPA) request on 19Oct2012 and a non-agreement letter was communicated on 05Dec2012 with the following key comments:

- The clinically relevant comparison is the proportion of patients with sustained remission between TCZ QW + 26 week prednisone taper and placebo QW + 52

week prednisone taper treatment groups. The placebo QW + 26 week prednisone taper group may be undertreated and this may invoke flare in some patients
- The definition of refractory patients should capture patients who continue to have active disease despite standard of care therapy
- Data from single trial to show efficacy in induction and maintenance of remission depends on robustness of data and support from secondary endpoints

Comments on the Statistical Analysis Plan were provided on 21Aug 2015 and 10June2016. These comments reiterated the concern regarding the primary endpoint; the addition of a non-inferiority assessment comparing TCZ to a 52 week prednisone taper did not completely ameliorate the concerns. Supportive analyses of the treatment effect of each component of the composite primary endpoint were requested. Superiority of TCZ + 26 week prednisone taper to placebo + 52 week prednisone taper was recommended as a secondary endpoint. In addition, the Agency again conveyed that the definition of disease flare, which could be made based on inflammatory markers alone, could bias results in favor of TCZ. The Applicant was also advised that if positive results on the flare endpoint are due to patients fulfilling ESR criteria rather than having signs or symptoms, the clinical meaningfulness of the results may be difficult to interpret.

A pre-sBLA Meeting was held 29Aug2016. Discussion focused on:
- Supportive analyses of the components of the primary endpoint
- Evaluation of the potential impact of immunogenicity on efficacy
- Justification for proposed dose should be based on any differences between treatment groups

Breakthrough therapy designation for the treatment of GCA was granted on 31Aug2016.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not impact the overall conclusions on safety and efficacy. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

3.2 Compliance with Good Clinical Practices

The Applicant certified that Study WA28119 was conducted in accordance with the principles of the "Declaration of Helsinki", the U.S. Food and Drug Administration regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and applicable local, state, and country laws. Appropriate Ethics Committees and Institutional Review Boards reviewed and approved the study. Audits were conducted by the Roche Clinical Quality Assurance group or designee at 6 investigator sites and 2 additional audits were performed by (b) (4) . No critical audit findings were observed. Study WA28119 was a multinational, multicenter study in which there were no outliers in response to suggest differential response by site, and therefore, an OSI inspection was not conducted.

3.3 Financial Disclosures

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. The Applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54.

Two subinvestigators reported disclosable financial interests. (b) (6), a subinvestigator at (b) (6) reported a disclosable financial interest based on initiation of an investigator-initiated study funded by Genentech, with a total payment to (b) (6) exceeding $25,000. The affiliated study site recruited (b) (6) in WA28119. (b) (6) participated in clinical assessments of signs and symptoms of Giant Cell Arteritis, but was not involved in consenting patients, determining inclusion/exclusion criteria, randomization, or dispensing medication. This is unlikely to have an effect on the outcome of the study given the randomized and blinded nature of treatment as well as the minimal contribution to study data. (b) (6) a subinvestigator at (b) (6), reported a disclosable financial interest related to a paid Genentech fellowship from (b) (6), with a total payment exceeding $25,000. The affiliated study site enrolled (b) (6) patients to Study WA28119. (b) (6) participated in clinical assessments and was not involved in consenting patients, determining inclusion/exclusion criteria, randomization, or dispensing medication. This is unlikely to have an effect on the outcome of the study given the randomized and blinded nature of treatment.

The Applicant initially reported 13 investigators or sub-investigators for which the Applicant was unable to obtain disclosure information, due to site closures. However, in a response to an information request dated 09Feb2017, the Applicant clarified that at least one financial disclosure form had been signed with no disclosable interests for each of the investigators or subinvestigators. The Applicant then identified a single investigator, Dr. Laura Liu, for whom a financial disclosure form was unable to be obtained because the study site was closed, however, in subsequent communication submitted 07March2017, the Applicant noted that a signed Financial Disclosure Form

was obtained from Dr. Liu dated 08Nov2012, stating she had no disclosable interests. Therefore, there are no investigators for whom financial disclosure information was not obtained.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original BLA applications.

4.2 Clinical Microbiology

No new clinical microbiology information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original BLA applications.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original BLA applications.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tocilizumab (TCZ) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1 subtype. It 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.

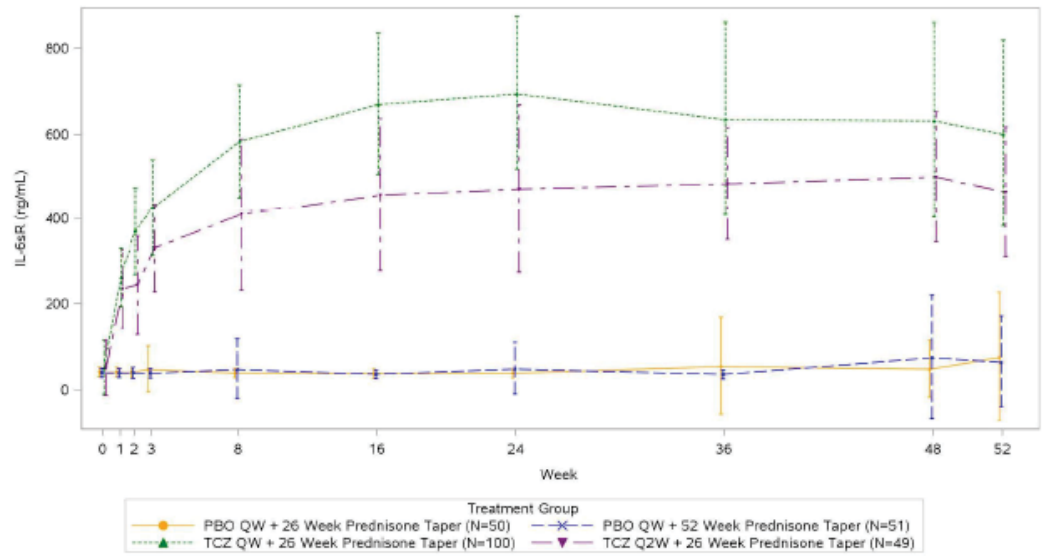
4.4.2 Pharmacodynamics

Changes in TCZ mechanism-related activity markers (IL-6 and sIL-6R) and markers of inflammation (CRP and ESR) were assessed in Study WA28119. A trend was observed for slightly higher increases (sIL-6R) and reductions (IL-6) in the PD parameters in the patients on the QW regimen, consistent with the higher C_{trough} (Figure 1A, Figure 1B). At Week 52, IL-6 levels were 25% higher in the TCZ QW group as compared to the Q2W group (65.99 ± 84.92 pg/mL vs. 52.70 ± 33.10 pg/mL), while levels of sIL-6R were 29% higher in the TCZ QW group (600.53 ± 217.52 ng/mL) as

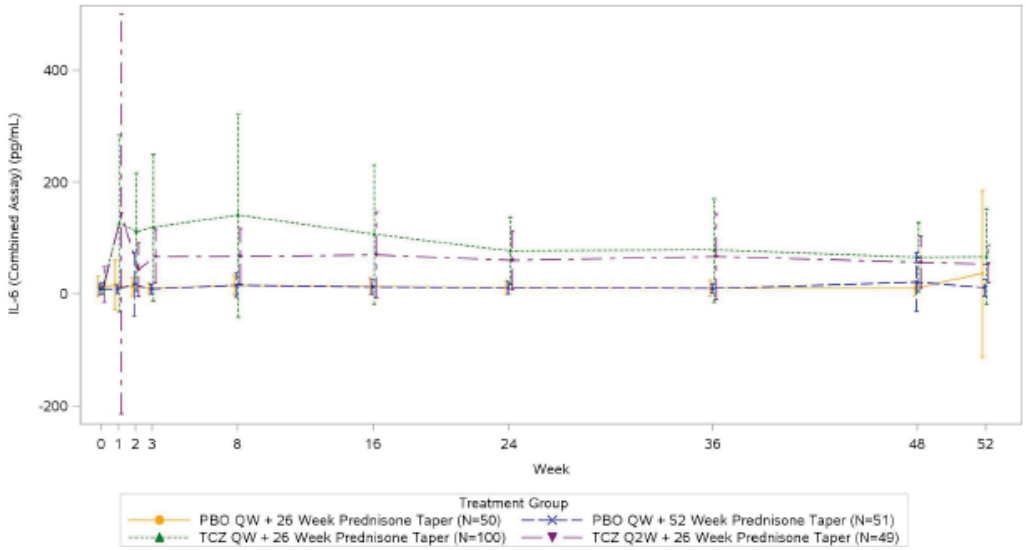
compared to the TCZ Q2W group (464.30 ± 153.64 ng/mL). Levels of sIL-6R in both dose groups were similar to the mean levels in RA patients (at Week 24) who received the same dose levels at steady state, despite the higher serum concentrations of TCZ in the GCA patients. Levels of sIL-6R and IL-6 in the placebo groups remained essentially unchanged from baseline at Week 52.

Figure 1: Pharmcodynamic parameters: Mean sIL-6R and IL-6 Levels by Visit

A. **Study WA28119: Mean ± SD soluble IL-6R Levels by Visit (TCZ QW, Q2W, PBO + 26 Week, PBO + 52 Week)**



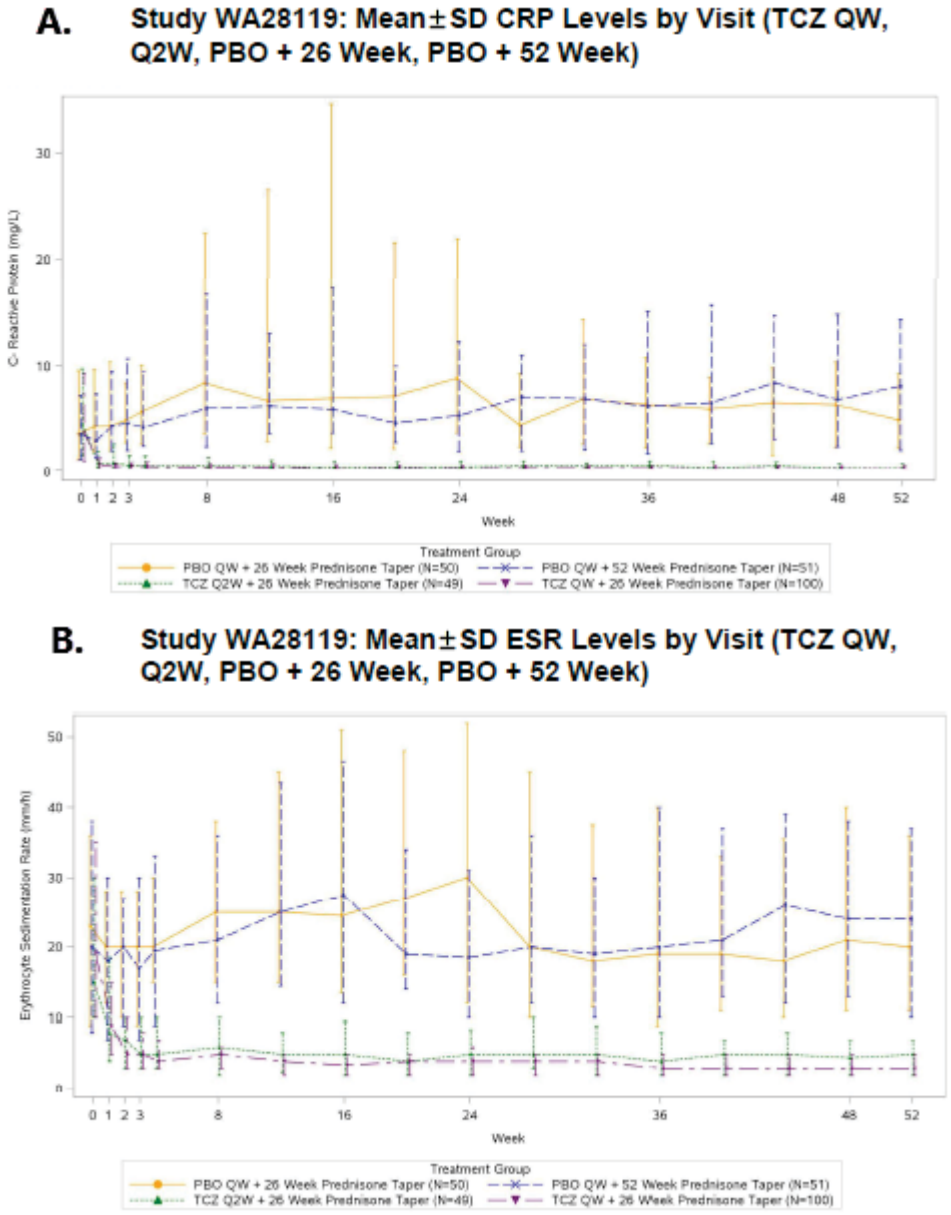
B. **Study WA28119: Mean ± SD IL-6 Concentrations by Visit (TCZ QW, Q2W, PBO + 26 Week, PBO + 52 Week)**



Source: Summary of Clinical Pharmacology, Figures 3-4

Mean CRP and ESR levels at baseline were near the upper range of normal; this is likely due to the use of glucocorticoids (prednisone 20-60 mg/day) at the time of the baseline assessment. Mean values of ESR and CRP decreased quickly in both TCZ treatment groups (Figure 2A, Figure 2B). At Week 52, mean CRP levels were 1.3 ± 4.1 and 0.8 ± 1.5 mg/L for the TCZ QW and Q2W groups, while mean ESR levels were 5.1 ± 5.8 and 5.6 ± 4.4 mm/h for the QW and Q2W groups, respectively. The mean CRP and ESR levels in the placebo groups at Week 52 were higher than those observed for the TCZ groups. In the PBO+26 wk treatment group, mean CRP and ESR were 8.0 ± 9.7 and 23.9 ± 19.1, respectively, while in the PBO+52 wk group, mean CRP was 11.2 ± 13.3 and mean ESR was 27.6 ± 22.5 at Week 52. Greater mean changes from baseline in ESR and CRP were observed in the TCZ treatment groups as compared to the placebo groups. The magnitude of the decrease in ESR favored the TCZ QW regimen, while the decrease in CRP favored the TCZ Q2W regimen.

Figure 2: Pharmacodynamic parameters: Mean CRP and ESR levels by visit



Source: Summary of Clinical Pharmacology, Figures 5-6

4.4.3 Pharmacokinetics

PK information is based on PK data from 149 GCA patients treated with TCZ QW or Q2W. Mean steady state TCZ concentrations were greater than dose-proportional after QW dosing compared to Q2W dosing. An approximate 6-fold and 2-fold accumulation in mean TCZ C_{trough} at steady state was observed in patients in the QW (67.93 ± 34.40 µg/ml) and Q2W (12.22 ± 10.02 µg/ml) treatment groups, respectively. Steady state C_{mean} for the TCZ QW regimen was 4.4 times higher than for the Q2W, and C_{max} was 3.8 times higher for TCZ QW. The increase in exposure between QW and Q2W dosing

is consistent with the known effect of concentration-dependent elimination of TCZ. The nonlinear elimination pathway is believed to represent target-medicated clearance process due to binding to soluble and membrane bound IL-6 receptors. Nearly complete target saturation was achieved at steady state during the dosing interval for the QW regimen, while the target-mediated elimination pathway was not saturated for the Q2W regimen, leading to high total clearance and high fluctuation of clearance over the dosing interval. Steady state exposure in the GCA population is approximately 50% higher than that in the RA population.

There was a trend for higher exposure in patients with lower body weight. Pearson's correlation coefficient was -0.504 for the TCZ QW regimen and -0.404 for the Q2W regimen, indicating a moderate inverse correlation between C_{trough} and body weight. Due to the effect of target mediated drug disposition in addition to the effect of body weight on clearance, steady state exposures following the Q2W regimen were more sensitive to body weight effects than the QW regimen. Body weight was the only covariate in the popPK model with an effect on the PK of TCZ. One third of the patients in WA28119 had moderate renal impairment with no significant impact on TCZ exposure.

C_{trough} was evaluated for differences between responders and non-responders. The mean ± standard deviation (SD) TCZ concentrations at Week 52 in responders was higher than that in non-responders in the TCZ QW group (69.18 ± 35.00 µg/mL and 64.89 ± 33.51 µg/mL) and TCZ Q2W group (13.26 ± 10.43 µg/mL and 8.95 ± 8.38 µg/mL). Throughout Part 1, the fraction of patients in remission was slightly lower in those patients in the lowest exposure tertile, and similar in the 2nd and 3rd tertiles, however the confidence intervals are overlapping. Results of a logistic regression analysis did not suggest a significant relationship between the probability of sustained remission with exposure. Based on a Cox proportional hazards analysis, time to first flare was shorter in patients in the lowest exposure tertile. Median cumulative glucocorticoid dose was not different based on TCZ exposure tertiles.

There was no association of TCZ concentration or exposure with SAEs, AEs in the SOC "Infections and Infestations" or AEs in the SOC "Gastrointestinal disorders." Consistent with the known TCZ exposure-dependent laboratory changes, there was a trend to greater decline of hematology parameters (white blood cells, neutrophils, and platelets) with increasing exposure in GCA patients, however there was no association of TCZ concentrations with occurrence of neutropenia or thrombocytopenia. Treatment-induced anti-drug antibodies (ADAs) were confirmed in 1 patient on the TCZ QW regimen and 3 patients on the Q2W regimen, however these did not appear to influence TCZ PK model parameters. In the two patients with non-neutralizing antibodies at baseline who later developed neutralizing ADAs, one patient had TCZ levels below the limit of quantification at Week 8 when neutralizing antibodies were identified, while the other patient had a decrease in TCZ levels at Week 52, though the neutralizing antibodies were observed at Weeks 24, 36, and 52. Therefore, a direct correlation between the presence of ADA and a decrease in exposure was not observed.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Studies in GCA

Study No. (Phase)	Study Design,	Population	No. of Patients	Dose, Route, and Regimen
Pivotal Phase III Study				
WA28119 (Phase III)	Multicenter, randomized, double-blind placebo-controlled superiority study to assess the efficacy and safety of TCZ in patients with GCA Part 1: 52-week blinded period for primary analysis Part 2: 104-week open-label extension to assess maintenance of disease remission and long-term safety in patients with newly diagnosed or relapsing GCA.	Patients ≥ 50 years with new-onset GCA and with relapsing GCA	251[a] (149 receiving TCZ)	162 mg SC TCZ (QW) + 26-week prednisone taper regimen 162 mg SC TCZ (Q2W) + 26-week prednisone taper regimen SC placebo + 26-week prednisone taper regimen SC placebo + 52-week prednisone taper regimen
Supporting Study				
ML25676 (Phase II)	Single-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of TCZ in the induction and maintenance of disease remission in patients with newly diagnosed or relapsing GCA	Patients ≥ 50 years with new-onset GCA and with relapsing GCA satisfying 1990 ACR criteria	30 (20 receiving TCZ)	8 mg/kg IV TCZ (13 infusions given in 4 week intervals until Week 52) + oral prednisolone (starting at 1 mg/kg per day) taper regimen IV placebo (13 infusions given in 4 week intervals until Week 52) + oral prednisolone (starting at 1 mg/kg per day) taper regimen

ACR: American College of Rheumatology; GC: glucocorticoids; GCA: Giant Cell Arteritis; IV: intravenous; QW: weekly; Q2W: every other week; SC: subcutaneous; TCZ: tocilizumab

[a] Of the 251 randomized patients, 1 patient who was randomized to the TCZ Q2W group withdrew the same day they were randomized, and did not receive any study treatment. This patient was excluded from the ITT population.

Source: Summary of Clinical Efficacy Table 1

5.2 Review Strategy

The supplemental BLA was reviewed for content, format, and overall data quality and integrity and found acceptable during the filing review.

Efficacy and safety analyses were derived from a single study conducted in GCA, Study WA28119. Efficacy and safety data in this submission were derived from Part 1 of WA28119, the completed placebo-controlled period. Limited safety data from 88 patients who had completed at least 100 weeks of follow up from the ongoing open label extension, Part 2, was also included in this submission. Efficacy analyses were performed on the intent-to-treat population, including all patients randomized into the study who received at least one TCZ/placebo injection. Efficacy analyses are summarized by treatment assigned at randomization. Safety analyses were performed on the safety population, including all patients who received at least one administration of study drug and provided at least one post-dose safety assessment. Safety data is summarized by actual treatment received. Disposition summaries are based on the all-patient population that includes all patients randomized in the study.

The Applicant also included data from Study ML25676, an investigator-initiated study of intravenous TCZ in combination with glucocorticoid treatment as compared to glucocorticoid treatment alone in the induction and maintenance of disease remission in 30 patients with new-onset or relapsing GCA. The Applicant provided summary data from this study, which was conducted with a different formulation, dose, and dosing regimen of tocilizumab. This study was reviewed as supportive and thus will be discussed separately under Study ML25676 below.

In addition, the Applicant submitted supportive safety data including:

- Pooled long-term safety data with IV TCZ in the RA population
- Background rates of AESI and glucocorticoid-induced toxicity information from an epidemiological analysis of the MarketScan health claims database
- Analysis of AEs reported in patients with GCA treated with IV TCZ outside of clinical trials

The Applicant has submitted pooled safety data with IV TCZ with justification that it represents the most comprehensive dataset in terms of number of patients who received TCZ and duration of individual follow-up. This is generally acceptable as the safety profile of SC TCZ was previously found to be the same as that of IV TCZ in RA during the review of the original BLA 125472 submission, with the exception of an increased incidence of injection site reactions (ISR) with SC TCZ.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol: WA28119

Title: A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in subjects with giant cell arteritis

Dates Conducted: The first patient was screened on 15July2013 and randomized on 22July2013. The last patient was randomized on 21April2015. The data cut-off date is 11April2016. The long term extension (Part 2) is ongoing.

Objectives:
Primary Objective:
To evaluate the efficacy of TCZ (QW and Q2W) compared to placebo, in combination with a 26-week prednisone taper regimen, in patients with GCA, as measured by the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined taper regimen

- Induction of remission had to occur within 12 weeks of randomization
- Remission was defined as the absence of flare (as defined below) and normalization of CRP (CRP <1 mg/dL)
- Sustained remission was defined as absence of flare following induction of remission up to the 52-week timepoint
    - Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or ESR ≥30 mm/h attributable to GCA
- Patients had to follow the protocol-defined prednisone taper regimen

Key Secondary Objective:
To evaluate the efficacy of TCZ (QW and Q2W) in combination with a 26-week prednisone taper regimen versus placebo in combination with the 52-week prednisone taper regimen in patients with GCA, as measured by the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined prednisone taper regimen

Secondary Objectives:

- To assess the efficacy of TCZ in combination with a 26-week prednisone taper regimen versus both placebo groups in patients with GCA, as measured by the following:
    - Time to GCA disease flare after clinical remission
    - Cumulative glucocorticoid dose (total sum of prednisone administered according to the protocol-defined tapering regimens plus the escape prednisone administered to treat GCA flares)
- To assess the effect on patient's quality of life of TCZ in combination with a 26-week prednisone taper regimen versus both placebo groups in patients with GCA based on the patient-reported outcome (PRO) as measured by SF-36 and patient global assessment (PGA) of disease activity on a visual analogue scale (VAS)

- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in combination with a 26-week prednisone taper regimen in patients with GCA

Exploratory Objectives:
Assessments of TCZ in combination with a 26-week prednisone taper versus both placebo groups on:

- Maintenance of remission in Part 2 of the study by evaluating proportion of patients in sustained remission at 64 weeks (and every 12 weeks thereafter)
- Annualized relapse rate
- Remission rates over time
- Fatigue as measured by Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) score
- Health economic score as measured by EuroQol 5D (EQ-5D) score
- Duration of glucocorticoid use by treatment group

Safety Objective:
To evaluate the safety and tolerability and immunogenicity of TCZ in combination with a 26-week prednisone taper regimen versus both placebo groups in patients with GCA

Overall Design:
Study WA28119 is a 156 week multicenter (76 sites in 14 countries), randomized, placebo-controlled, double-blind, parallel-group study with a planned enrollment of 250 patients with new-onset and relapsing GCA. New-onset GCA was defined as GCA diagnosed within 6 weeks of the baseline visit and relapsing GCA was defined as GCA diagnosed >6 weeks before baseline and previous treatment with ≥40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at any time. Enrollment of relapsing patients was preferentially limited to 70% but could be increased based on rate of enrollment of new-onset versus relapsing.

A 52 week double blind treatment period (Part 1) was followed by a 104-week open-label period (Part 2). Following a screening period of up to 6 weeks, during which time patients could receive glucocorticoids for treatment of GCA at the discretion of the investigator, patients were randomized 1:1:2:1 by interactive voice/web-based response system to receive one of the following treatment regimens:

- Placebo SC weekly (QW)+26-week prednisone taper regimen (PBO+26wk; n=50)
- Placebo SC QW+52-week prednisone taper regimen (PBO+52wk; n=50)
- 162 mg TCZ SC QW+26-week prednisone taper regimen (TCZ QW; n=100)
- 162 mg TCZ SC every other week (Q2W)+26-week prednisone taper regimen (TCZ Q2W; n=50)

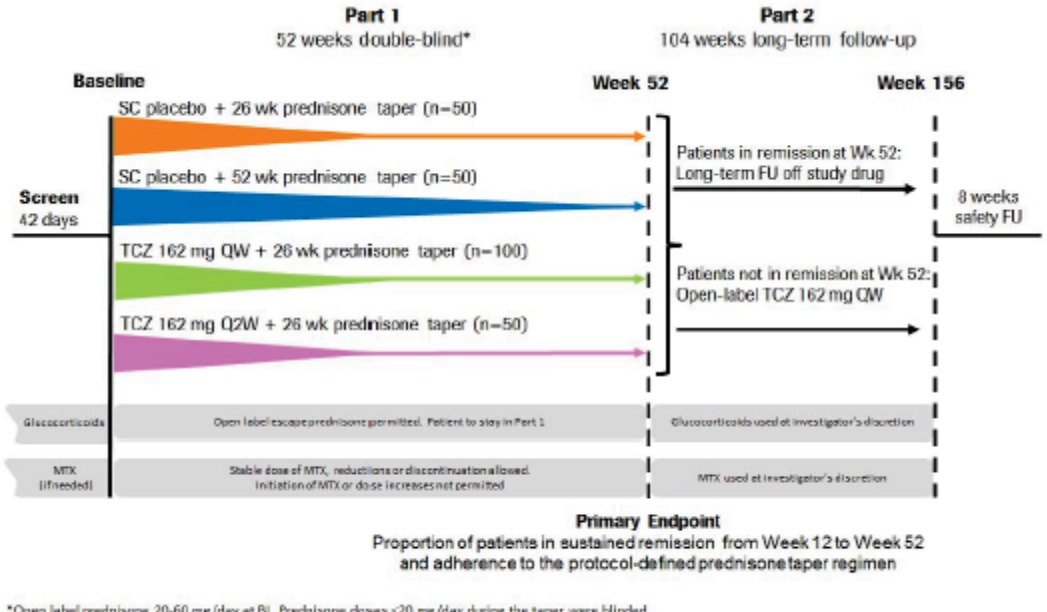
Randomization was stratified by baseline prednisone dose (>30 mg/day and ≤30 mg/day). At the time of the baseline visit, the daily prednisone dose had to be within the range of 20-60 mg/day. Prednisone tapering was performed in an open-label manner to a daily dose of 20 mg/day (inclusive), and then double-blind over-encapsulated

capsules were provided to patients in weekly numbered blister packs for dosages below 20 mg. Depending on the assigned taper regimen, the daily encapsulated dose could contain prednisone capsules, placebo capsules, or a combination of the two.
The composition of the investigational TCZ was the same as that of the currently marketed product. Blinded TCZ/PBO pre-filled syringe (PFS) was provided for Part 1 of the study. Study drug was supplied in boxes containing two 1 mL PFS with needle safety device, labeled 1 and 2; patients were instructed to use the PFS in the correct order of PFS labeled 1 followed by PFS labeled 2 the next week. Open-label TCZ PFS was provided for Part 2.

Patients and caregivers received injection training at the initial treatment. The first four SC injections in the double-blind period were administered under close supervision of the investigator and patients were required to remain at the sites for approximately 2 hours following each SC injection. Recommended injection sites were front of thighs, lower abdomen below the navel, except for the 5 cm area directly around the navel, and, if a caregiver was administering the injection, the outer area of the upper arms could be used. After the first two injections and after demonstrating competence, the patient or caregiver could administer subsequent SC injections, and after the first four injections, the injections could be administered at home. If the patient was unable or did not wish to administer study drug at home, clinic staff could administer the injections to the patient. Minimum and maximum intervals between the blinded weekly injections were 5 days and 11 days, respectively. If the 11 day maximum interval had passed, the dose was considered missed, and the next dose taken was to be the next scheduled dose as per the schedule of assessments.

The figure below details the study scheme:

Figure 3: Study scheme



*Open label prednisone 20-60 mg/day at BL. Prednisone doses <20 mg/day during the taper were blinded
BL, baseline; FU, follow up; MTX, methotrexate; QW, weekly; Q2W, every other week; SC, subcutaneous; TCZ, tocilizumab.

Source: Clinical Study Report Figure 1

Part 1

During the double-blind period, patients had visits at Week 1, 2, 3, and 4, and then every 4 weeks according to the Appendix 2: Schedule of Assessments. At each visit, disease activity and ability to adhere to protocol-defined prednisone taper schedule was assessed. Separate Clinical and Laboratory Assessors were used to maintain the blinding. The evaluation of clinical signs and symptoms by the Clinical Assessor included the following:

- Fever (≥38°C or 100.4°F)
- Symptoms of PMR (morning stiffness and/or pain, in the shoulder and/or hip girdles)
- Localized headache, temporal artery or scalp tenderness
- Visual signs or symptoms such as acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy (A-AION), transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes)
- Jaw or mouth pain
- New or worsened extremity claudication
- Other features judged by the Clinical Assessor to be consistent with a GCA or PMR flare

In addition, patients will assess their disease activity using the VAS scale.

Source: Study WA28119 Protocol Version 4, Section 4.5.1.5.1

As discussed above, remission was defined as the absence of flare and normalization of the CRP (<1 mg/dL). Sustained remission was defined as the absence of flare following induction of remission within 12 weeks of randomization and maintained from Week 12 up to Week 52. Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or ESR ≥ 30 mm/h attributable to GCA. Therefore, a patient could have signs and symptoms of GCA and/or an elevated ESR attributed to GCA present at a study visit and still be considered in remission if the investigator determined the findings were not severe enough to be considered a flare.

The Clinical Assessor was blinded to the results of ESR and CRP after the baseline visit. The Laboratory Assessor was responsible for the overall clinical management of the patient outside their GCA and was permitted to discuss ESR elevations pre-specified in the Dual Assessor Manual with the Clinical Assessor as required for clinical management of the patient. The Laboratory Assessor was blinded to CRP after the baseline visit. The Laboratory Assessor was also responsible for risk mitigation for neutropenia, thrombocytopenia, and elevated liver enzymes as specified in the protocol. Unblinding occurred at the time of the Week 52 primary analysis, or in the event of unexpected serious adverse events considered by the investigator to be related to study drug.

Escape Therapy
During the open-label prednisone taper, patients who experienced a disease flare or who were unable to adhere to the prednisone tapering schedule due to persistent disease activity, received open-label escape prednisone based on an investigator defined regimen; these patients did not enter the double-blind taper phase. During the double-blind taper phase, patients who experienced a disease flare or who were unable to adhere to the prednisone tapering schedule, received open-label escape prednisone therapy at a dose of ≥20 mg/day and continued on an investigator-defined prednisone schedule. The patients who received escape therapy with prednisone continued to receive blinded TCZ or placebo injections and study assessments as per the schedule of assessments for the entire 52 weeks of Part 1. These patients could subsequently enter Part 2 of the study.

PK Substudy
Pre-dose samples for serum TCZ concentrations, CRP, ESR, and IL-6 and sIL-6R levels, as well as for immunogenicity, were collected for all patients. A PK substudy to enroll a planned total of 35 patients was conducted at selected sites. PK samples were obtained at the first SC dose and after the Week 16 dose from patients in the substudy at a ratio of approximately 6:6:12:6 from the PBO+26wk, PBO+52wk, TCZ QW, and TCZ Q2W treatment groups, respectively.

Part 2
Based on the investigator's assessment of disease activity at the end of Part 1, patients can be treated with open-label TCZ 162 mg QW if there is persistent disease activity/flare, or patients can be followed off treatment for maintenance of established

remission. GCA therapy can be adjusted at any time during Part 2, including initiation/discontinuation of open-label TCZ 162 mg QW, and/or changes to glucocorticoids or MTX treatment, at the discretion of the investigator and on the basis of disease activity. Patients who initiate open-label TCZ attend weekly visits for the first 4 injections, and therefore, patients initiating open-label TCZ are monitored more frequently than those not receiving TCZ in Part 2.

Safety
Safety assessments included AEs, standard laboratory assessments, physical examination, vital signs, and immunogenicity. The protocol specifies risk mitigation and dose modification rules for events including interruption of dosing for serious infections, assessment of a potential demyelination event, neutropenia with ANC 500-1000 cells/mm^3, thrombocytopenia with platelet count 50,000-100,000 cells/mm^3, and AST or ALT values >1 to 3x upper limit of normal (ULN) or >3 to 5x ULN.

Reasons for study treatment discontinuation include: pregnancy, GI perforations, neutropenia <500 cell/mm^3 with repeat confirmation, thrombocytopenia <50,000 cell/mm^3 with repeat confirmation, elevated liver enzymes ALT or AST >3x ULN with other signs and symptoms and laboratory abnormalities as specified in the protocol, malignancies (except local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix status post excision and cure), or anaphylaxis or serious hypersensitivity.

An independent Data Monitoring Committee (iDMC) performed regular reviews of the safety data as detailed in the Charter for the iDMC.

Patients can be discontinued from the study drug or withdrawn at any time by the patient or the investigator. Other reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to: withdrawal of consent, any medical condition the investigator or Sponsor determines may jeopardize the patient's safety by remaining in the study, best interest of the patient in the opinion of the investigator or Sponsor, or patient non-compliance.

Patients who discontinue early from the study will complete an early withdrawal visit. All patients will have follow-up visits at 4 weeks and 8 weeks after the end of treatment or the early withdrawal visit to assess for AEs and concomitant medications.

Eligibility:
Major Inclusion Criteria:

1. Must be able and willing to provide informed consent and comply with study protocol
2. Diagnosis of GCA based on the following criteria:
    - Age ≥50 years
    - History of ESR ≥50 mm/hour (if historic ESR unavailable, history of CRP ≥2.45 mg/dL required)
    - **AND** at least one of the following:

- Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)
- Symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

- **AND** at least one of the following:
  - Temporal artery biopsy revealing features of GCA
  - Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRA, CTA, or PET-CT

3. New-onset or relapsing active disease defined as follows:
   - New-onset: diagnosis of GCA within 6 weeks of baseline visit
   - Relapsing: diagnosis of GCA >6 weeks before baseline visit and previous treatment with ≥40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at any time
     - The 6 week window calculated from date of suspected GCA diagnosis, defined as the data when glucocorticoid therapy initiated to treat suspected GCA

   AND
   - Active GCA within 6 weeks of baseline visit (active disease defined as the presence of clinical signs and symptoms [cranial or PMR] and ESR ≥ 30 mm/hr or CRP ≥ 1 mg/dL). ESR ≥ 30 mm/hr or CRP ≥ 1 mg/dL not required if active GCA confirmed by positive temporal artery biopsy within 6 weeks of baseline visit

Major Exclusion Criteria:

General Exclusion Criteria:

1. Major surgery within 8 weeks prior to screening or planned major surgery within 12 months after randomization
2. Transplanted organs (except corneal transplant performed more than 3 months prior to screening)
3. Major ischemic event, unrelated to GCA, within 12 weeks of screening

Exclusions Related to Prior or Concomitant Therapy

4. Treatment with any investigational agent within 12 weeks (or 5 half-lives of the investigational drug, whichever was longer) of screening
5. Previous treatment with cell-depleting therapies, including investigational agents, including but not limited to Campath (alemtuzumab), anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20
6. Treatment with IV gamma globulin or plasmapheresis within 6 months of baseline
7. Previous treatment with alkylating agents, such as chlorambucil, or with total lymphoid irradiation
8. Previous treatment with TCZ
9. Immunization with a live/attenuated vaccine within ≤ 4 weeks prior to baseline
10. Treatment with hydroxychloroquine, cyclosporine A, azathioprine, or mycophenolate mofetil (MMF) within 4 weeks of baseline
11. Treatment with etanercept within 2 weeks; infliximab, certolizumab, golimumab, abatacept, or adalimumab within 8 weeks; or anakinra within 1 week of baseline
12. Previous treatment with tofacitinib
13. Treatment with cyclophosphamide within 6 months of baseline

14. Patients requiring systemic glucocorticoids for conditions other than GCA, which, in the opinion of the investigator, would interfere with adherence to the fixed glucocorticoid taper regimen and/or to assessment of efficacy in response to the test article
15. Chronic use of systemic glucocorticoids for > 4 years or inability, in the opinion of the investigator, to withdraw glucocorticoid treatment through protocol-defined taper regimen due to suspected or established adrenal insufficiency
16. Receipt of > 100 mg daily intravenous methylprednisolone within 6 weeks of baseline

Exclusions Related to General Safety

17. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies or to prednisone
18. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), psychiatric, osteoporosis/osteomalacia, glaucoma, corneal ulcers/injuries, or GI disease
19. Current liver disease, as determined by the investigator
20. History of diverticulitis, diverticulosis requiring antibiotic treatment, or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose a patient to perforations
21. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis [TB] and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of the nail beds)
22. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks of screening
23. Active TB requiring treatment within the previous 3 years
    Patients were to be screened for latent TB and, if positive, treated according to local practice guidelines prior to initiating TCZ treatment. Patients treated for TB with no recurrence within 3 years and patients treated for latent TB within 3 years were eligible.
24. Primary or secondary immunodeficiency (history of or currently active)
25. Evidence of malignant disease or malignancies diagnosed within the previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that had been excised and cured)
26. Females of childbearing potential and females who were breastfeeding
27. Males of reproductive potential who were not willing to use an effective method of contraception, such as condom, sterilization, or true abstinence throughout study and for a minimum of 6 months after study drug therapy
28. History of alcohol, drug, or chemical abuse within 1 year prior to screening
29. Body weight > 150 kg

Laboratory Exclusions (at Screening)

30. Serum creatinine > 1.4 mg/dL (124 µmol/L) in female patients and > 1.6 mg/dL (141 µmol/L) in male patients
31. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × Upper limit of normal (ULN)
32. Total bilirubin > ULN
33. Platelet count < 100×10^9/L ($100{,}000/mm^3$)
34. Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
35. White blood cells < 3.0×10^9/L ($3000/mm^3$)

36. Absolute neutrophil count < 2.0 × 10^9/L (2000/mm^3)
37. Absolute lymphocyte count < 0.5 × 10^9/L (500/mm^3)
38. Positive hepatitis B surface antigen or hepatitis C antibody

Concomitant Medications:
Patients in all arms were treated with anti-platelet therapy (aspirin or clopidogrel) according to local practice and investigator discretion. Use of lipid lowering agents in patients with elevated lipids was strongly encouraged in conjunction with the investigator's clinical judgment and guidelines.

Patients received oral calcium and 25-OH vitamin D supplementation (1200-1500 mg and 800-1000 IU daily in divided doses, respectively) for prevention of glucocorticoid-induced osteoporosis in the absence of contraindications. Additionally bisphosphonate therapy (alendronate 70 mg weekly or zolendronate 4 mg annually) was administered at the discretion of the investigator unless contraindicated. Patients with documented osteoporosis were treated with approved treatments according to local practice or clinical guidelines.

Concomitant methotrexate (MTX) was permitted if it was started prior to screening, but the dose was to remain stable and not increased throughout the screening and double-blind periods of the study. If necessary, MTX could be reduced or discontinued during Part 1. During Part 2, MTX could be initiated or adjusted at the discretion of the investigator.

Patients could receive additional short-term corticosteroids in addition to the protocol-defined prednisone taper during Part 1 if necessary for the management of the patient, for events such as serious infection, or when required to prevent adrenal insufficiency. Intra-articular, intravenous, or intramuscular corticosteroids were not permitted. In Part 2, corticosteroids could be administered at the discretion of the investigator.

Prohibited therapies include treatment with any investigational agent, cell-depleting therapies, biologic agents, Janus kinase inhibitors, alkylating agents, bone marrow transplantation with total lymphoid irradiation, thalidomide, IV gamma globulin, antithymocyte globulin, plasmapheresis, or extracorporeal photopheresis and azathioprine. Immunization with a live or attenuated vaccine is prohibited within 4 weeks of baseline through 12 weeks after the last administration of study drug.

Endpoints:
Primary efficacy endpoint: The proportion of patients in sustained remission at Week 52 in the TCZ treatment groups vs. the placebo group with 26-week prednisone taper

Key secondary endpoint: The proportion of patients in sustained remission at Week 52 in the TCZ treatment groups vs. the placebo group with 52-week prednisone taper

Other secondary efficacy endpoints:

- Time to first GCA disease flare after clinical remission (up to 52 weeks)
- Summary of total cumulative prednisone dose over 52 weeks
- Change from baseline in SF-36 (Physical and Mental Component Summaries) at 52 weeks
- Change from baseline in PGA of disease activity (VAS) scale at 52 weeks

Other endpoints:

- Safety
- PD
- PK

Statistics

A sample size of 100 patients in the 162 mg TCZ QW group and 50 patients in the 162 TCZ q2W and PBO+26 wk group were estimated to provide 90% power to detect a difference in the proportion of patients in sustained remission at Week 52 for both TCZ arms versus placebo at an overall alpha level of 0.01 (2 sided). This calculation was based on the assumption that the absolute difference in proportion of patients in sustained remission at Week 52 was 40%.

Two independent hierarchies for the TCZ dose families for which the overall alpha level was equally divided corrected for the type I error rate for multiple comparisons. In addition, comparisons were tested in a fixed sequence to further control for multiplicity.

- Hierarchy 1 tested the primary endpoint for superiority of TCZ QW+26 wk prednisone taper versus placebo + 26 wk prednisone taper, followed by the key secondary endpoint for non-inferiority of TCZ QW+26 wk prednisone taper vs. placebo+52 wk prednisone taper
- Hierarchy 2 tested the primary endpoint for superiority of TCZ Q2W + 26 wk prednisone taper vs. placebo + 26 wk prednisone taper, followed by the key secondary endpoint for non-inferiority of TCZ Q2W + 26 wk prednisone taper vs. placebo + 52 wk prednisone taper

Statistical significance could not be claimed if the preceding test for superiority did not have a significant p-value (<0.005).

Analysis of the primary endpoint, the proportion of patients in sustained remission at Week 52, was analyzed using a Cohran-Mantel-Haenszel (CMH) test and adjusted for starting prednisone dose (≤ 30 mg/day, > 30 mg/day). Sensitivity analyses included tipping point analysis for sustained remission, and an analysis on the basis of signs and symptoms of disease (excluding the requirement for normalization of CRP from definition of remission). The following were considered non-responders for the primary and key secondary endpoints: patients who did not achieve remission within 12 weeks of baseline, those who had a flare and/or received escape therapy, those who did not adhere to the prednisone taper regimen, those who withdrew from the study prior to Week 52, those who had elevated CRP values at two consecutive visits from Week 12 onwards, and those for whom remission status could not be determined at Week 52.

Analysis of the key secondary endpoint, proportion of patients in sustained remission at Week 52 in the TCZ groups in combination with a 26-wk prednisone taper regimen compared with the placebo+52 wk prednisone taper group, was a noninferiority test in which the TCZ groups were considered as non-inferior to the placebo + 52 wk taper if the lower bound of the two-sided 99.5% CI was ≥ -22.5% (M2), where M2 represents 50% of the entire steroid-only effect. The non-inferiority margin was selected to preserve at least 50% of a minimum treatment effect of 45% observed with corticosteroid therapy alone. Testing for superiority was planned if non-inferiority was met within the hierarchy. The analysis of the difference in proportions was performed using a CMH test based on the normal approximation adjusted for the baseline prednisone dose. Testing for superiority was planned if non-inferiority was met within the hierarchy.

All other secondary endpoints were not formally tested. Time to first GCA disease flare after clinical remission up to Week 52 was assessed using Cox proportional hazards model adjusting for the stratification factor applied at randomization. Patients who withdrew from the study prior to Week 52 were censored from the time of withdrawal. Total cumulative prednisone dose over 52 weeks was analyzed using a van Elteren test stratified by starting prednisone dose. For records of missed tablets from the protocol-defined prednisone taper, the missed tablets were assumed to be the minimum dose tablets available from that pack, resulting in a conservative overestimation of prednisone dose on all treatment arms. Patients who received commercial prednisone administered by oral, intravenous, intramuscular, intra-arterial, subcutaneous, and 'other' routes of administration were included in the analysis of cumulative prednisone dose.

Protocol Amendments & Study Conduct:
There were 3 amendments to the original protocol (dated 20July2012). Amendments Version 2, Version 3, and Version 4 Canada were made prior to screening of the first patient on 15July 2013. Key changes in protocol Version 2, 3, and Version 4 Canada are as follows:
In Version 2 (19Oct 2012):

- Inclusion and exclusion criteria were clarified including requirement of history of ESR ≥ 50 mm/hr for diagnosis of GCA, exclusion of only major ischemic events unrelated to GCA, and exclusion of patients who received pulsed methylprednisolone within 6 weeks of baseline
- Definition of remission clarified (absence of signs and symptoms attributable to GCA and normalization of ESR (<30 mm/hr) and CRP (<1 mg/dL))
- Addition of lipid lowering agents as permitted concomitant medications
- All patients eligible for treatment in Part 2 regardless of compliance during Part 1

In Version 3 (08Feb 2013):

- Definition of relapsing patients updated to include those with active disease despite at least 2 consecutive weeks of treatment with ≥ 40 mg/day prednisone at any time to ensure all relapsing patients adequately treated prior to study entry

- Revision of endpoints after FDA SPA feedback to add comparison of proportion of patients in sustained remission at Week 52 in the TCZ treatment groups as compared to the placebo + 52 week prednisone taper (key secondary endpoint)
- Addition of exclusion criterion of prohibition of previous treatment with tofacitinib

In Version 4 Canada (07June 2013):

- At the request of Health Canada, clarification was made to standard of care for glucocorticoid treatment in patients with new-onset GCA during the screening period.

On 22January 2014, Version 4 (Version 5 Canada) included the following key changes:

- Revision of flare definition to allow clinical assessor to consider an elevated ESR as disease flare in the absence of GCA signs and symptoms if it is attributable to GCA in the opinion of the investigator. This does not apply to CRP. The definition of remission was also modified to reflect this change
- Addition of CRP ≥ 2.45 mg/dL as inclusion criterion for patients where historic ESR value is unavailable
- Removal of requirement for elevated inflammatory markers to confirm active disease in patients with a positive temporal artery biopsy within 6 weeks of baseline
- Clarification that new-onset GCA is defined as *suspected* GCA diagnosis (defined as when corticosteroids initiated to treat suspected GCA) within 6 weeks of baseline visit
- Clarification use of intra-articular, intravenous, and intramuscular corticosteroids are not permitted
- Update of time window required for a latent tuberculosis test to be performed prior to initiation of study drug treatment increased from 3 weeks to 6 weeks

Protocol Versions 2, 3, and Version 4 Canada were instituted prior to the screening of the first patient and therefore, these changes did not influence safety and efficacy analyses. In protocol Version 4 (Version 5 Canada), change to the definition of flare to include an elevated ESR in the absence of signs and symptoms of GCA could impact the efficacy results, as TCZ is known to have a pharmacodynamic effect on ESR and CRP. This could potentially bias the results in favor of TCZ if there is an imbalance of flares defined by elevated ESR only in the placebo groups. Sensitivity analyses were conducted to evaluate the proportion of flares that were based on signs and symptoms of GCA, those based on ESR ≥ 30 mm/hr, and those based on both symptoms and lab criteria. Other key changes in this version increase the likelihood of selecting for patients with active disease and decrease the potential for disease improvement from uncontrolled additional steroids; these changes are unlikely to impact safety and efficacy results in an unbalanced fashion.

6 Review of Efficacy

6.1 Indication

The Applicant's proposed indication is for the treatment of adult patients with Giant Cell Arteritis. The proposed dose is 162 mg weekly.

6.1.1 Methods

Support for efficacy is derived from Study WA28119, a double-blind, placebo-controlled, parallel-group study in patients with new-onset and relapsing GCA, randomized to two dosing regimens of TCZ or placebo, in addition to a standardized prednisone taper regimen. The primary analysis population for all efficacy analyses was the Intent-to-Treat (ITT) population, which included all patients randomized into the study who received at least one TCZ/placebo injection. The safety population included all patients who received at least one administration of study drug and provided at least one post-dose safety assessment. Safety data is summarized by actual treatment received. The escape population included all patients who received at least one dose of TCZ/placebo SC study drug, entered escape therapy, and received at least one dose of escape prednisone. For details of the statistical analysis, refer to the discussion on Statistics in Section 5 above.

6.1.2 Demographics

The majority of patients were Caucasian (96.8%), female (74.9%) with a mean age of 69 years, representative of the population of patients with GCA. Approximately 20% of the patients were enrolled at sites in the United States, and the remainder of the patients were enrolled in Europe (79.3%) and Canada (0.8%). Baseline demographics were generally balanced between treatment groups (Table 2), with the exception of smoking status. A greater proportion of patients in the PBO+26 wk treatment group were never smokers (70%) as compared with the other treatment groups (approximately 57% in each group). The patient demographic characteristics were balanced and representative of the intended patient population.

Table 2: Summary of Demographic Data at Baseline (All Patients)

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Age (years)				
n	50	51	100	50
Mean (SD)	69.3 (8.1)	67.8 (7.7)	69.5 (8.5)	69.4 (8.2)
Median	70.5	68.0	71.0	71.0
Min - Max	52 - 83	52 - 84	51 - 85	53 - 91
Age group (years)				
n	50	51	100	50
< 65 years	16 (32.0%)	17 (33.3%)	32 (32.0%)	17 (34.0%)
>= 65 years	34 (68.0%)	34 (66.7%)	68 (68.0%)	33 (66.0%)
Sex				
n	50	51	100	50
Male	12 (24.0%)	14 (27.5%)	22 (22.0%)	15 (30.0%)
Female	38 (76.0%)	37 (72.5%)	78 (78.0%)	35 (70.0%)
Ethnicity				
n	50	51	100	50
Hispanic or Latino	0	1 (2.0%)	2 (2.0%)	1 (2.0%)
Not Hispanic or Latino	49 (98.0%)	49 (96.1%)	96 (96.0%)	46 (92.0%)
Not Reported	0	1 (2.0%)	2 (2.0%)	2 (4.0%)
Unknown	1 (2.0%)	0	0	1 (2.0%)
Race				
n	50	51	100	50
Asian	0	0	0	1 (2.0%)
Black or African American	0	2 (3.9%)	1 (1.0%)	0
Other	0	0	1 (1.0%)	1 (2.0%)
White	50 (100.0%)	49 (96.1%)	97 (97.0%)	47 (94.0%)
Unknown	0	0	1 (1.0%)	1 (2.0%)
Weight (kg)				
n	50	51	100	49
Mean (SD)	70.12 (15.83)	73.13 (15.34)	69.82 (13.82)	70.84 (16.09)
Median	66.65	70.60	67.50	69.20
Min - Max	47.7 - 120.0	48.5 - 108.0	48.0 - 105.0	46.4 - 124.1
Height (cm)				
n	50	51	100	49
Mean (SD)	164.70 (9.51)	167.86 (8.45)	163.90 (10.08)	165.33 (9.09)
Median	162.80	167.00	163.00	167.70
Min - Max	139.7 - 188.0	153.0 - 191.0	125.3 - 187.0	139.0 - 184.0
BMI (kg/m2)				
n	50	51	100	49
Mean (SD)	25.70 (4.46)	25.80 (4.13)	25.97 (4.42)	25.99 (6.15)
Median	24.92	25.35	25.62	24.80
Min - Max	18.0 - 40.1	18.3 - 36.0	18.1 - 38.6	17.8 - 53.4
Smoking History				
n	50	51	100	49
Never	35 (70.0%)	29 (56.9%)	57 (57.0%)	28 (57.1%)
Current	7 (14.0%)	9 (17.6%)	13 (13.0%)	5 (10.2%)
Previous	8 (16.0%)	13 (25.5%)	30 (30.0%)	16 (32.7%)

Source: Adapted from Clinical Study Report Table 10

Patients met criteria for GCA as defined in the inclusion criteria and presented in Table 3. Approximately, 78.5% of patients met ACR classification criteria for GCA (Hunder, 1990). All patients were ≥50 years and 96% of patients had a history of ESR ≥50 mm/hr, while 83% had a history of a CRP ≥2.45 mg/dL. New-onset localized headache (67.3%) was the most frequent cranial symptom of GCA, while 62.2% of patients reported symptoms of polymyalgia rheumatica (PMR). Approximately 10% of patients

experienced ischemia-related visual loss. Characteristics at diagnosis were generally balanced across the treatment groups with a somewhat greater proportion of patients in the TCZ Q2W group with temporal artery tenderness, while fewer TCZ QW patients experienced decreased temporal artery pulsation. A greater proportion of patients in the PBO+26 wk and TCZ Q2W groups had ischemia-related vision loss and otherwise unexplained mouth or jaw pain upon mastication, although these differences are due to small numbers of patients as presented in Table 3. The diagnosis of GCA was confirmed by temporal artery biopsy in 62.2% of the overall population, while imaging results were positive in 45.8% of the patients. Of the 115 patients with a positive imaging result, 94 (81.7%) patients had a positive imaging result with either a negative temporal artery biopsy or without a temporal artery biopsy performed. Patients diagnosed by imaging alone, in the absence of cranial symptoms and a positive biopsy, were balanced across the treatment groups (PBO+26 wk: 16.0%, PBO+52 wk: 13.7%, TCZ QW 18.0%, TCZ Q2W 18.0%).

Table 3: Summary of GCA Disease Features at Diagnosis (All Patients)

	PBO+26 wk N = 50 n (%)	PBO+52 wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 50 n (%)
Age ≥50 years	50 (100.0)	51 (100.0)	100 (100.0)	50 (100.0)
History of ESR ≥50 mm/hour	49 (98.0)	51 (100.0)	94 (94.0)	47 (94.0)
History of CRP ≥2.45 mg/dL	41 (82.0)	38 (74.5)	87 (87.0)	43 (86.0)
Cranial Symptoms				
New-onset localized headache	29 (58.0)	34 (66.7)	68 (68.0)	38 (76.0)
Scalp tenderness	16 (32.0)	16 (31.4)	38 (38.0)	20 (40.0)
Temporal artery tenderness	14 (28.0)	14 (27.5)	26 (26.0)	18 (36.0)
Temporal artery decreased pulsation	8 (16.0)	6 (11.8)	7 (7.0)	8 (16.0)
Ischemia-related vision loss	7 (14.0)	4 (7.8)	7 (7.0)	7 (14.0)
Otherwise unexplained mouth or jaw pain upon mastication	20 (40.0)	15 (29.4)	31 (31.0)	19 (38.0)
Symptoms of PMR	30 (60.0)	35 (68.6)	59 (59.0)	32 (64.0)
Temporal artery biopsy performed	38 (76.0)	33 (64.7)	64 (64.0)	37 (74.0)
Positive temporal artery biopsy	36 (94.7)	29 (87.9)	57 (89.1)	34 (91.9)
Positive imaging study	19 (38.0)	23 (45.1)	50 (50.0)	23 (46.0)
Diagnosis by imaging with no biopsy performed or negative biopsy	14 (28.0)	21 (41.2)	43 (43.0)	16 (32.0)

Source: Adapted from Clinical Study Report Table 11
Reviewer JMP analysis, ABASE dataset using terms HTAB, HTABP, LVVP, LVVOFL, LVVONCFL, HCRAN, TRT01P

Protocol Version 4 (Version 5 Canada) updated the inclusion criterion such that patients with a CRP ≥2.45 mg/dL were eligible for enrollment in those patients where historic ESR value was unavailable. Ten patients did not have a historical ESR ≥50 mm/hr. Of these, all 10 had a historical CRP ≥2.45, 7 had a positive temporal artery biopsy, while 3 (2 TCZ QW, 1 PBO+26 wk) were diagnosed by imaging. These characteristics, in addition to clinical symptoms of either new-onset localized headache (8 patients) or PMR (5 patients) in all 10 patients, support the diagnosis of GCA in these patients without a historical ESR.

Table 4 presents a summary of the baseline disease characteristics. At baseline, the median duration of GCA ranged from 41.5 days in the TCZ Q2W treatment group to 80.0 days in the PBO+26 wk treatment group. The proportion of patients with new-onset versus relapsing disease was well balanced across the PBO+26 wk, PBO+52 wk, and TCZ QW treatment groups, while the TCZ Q2W treatment group included more patients with new-onset GCA and fewer patients with relapsing disease as compared to the other treatment groups.

The proportions of patients with cranial symptoms only, PMR symptoms only, and both cranial and PMR symptoms were generally balanced across the treatment groups. Vision impairment at baseline was reported in few patients: blurred vision (14 patients), unilateral blindness (4 patients), amaurosis fugax (2 patients), ischemic optic neuropathy (2 patients), and bilateral blindness (1 patient). Amaurosis fugax and ischemic optic neuropathy were reported in 1 patient in each of the TCZ treatment groups, while 1 patient in each treatment group had unilateral blindness and 1 patient in the TCZ Q2W group had bilateral blindness.

The median baseline ESR was lower in the TCZ Q2W (15.0 mm/hr), as compared to the other treatment groups in which the median baseline ESR ranged from 19.0 (TCZ QW) to 23.0 mm/hr (PBO+26 wk), however the median baseline CRP was higher in the TCZ Q2W group (4.5 mg/L) as compared to the other groups (Table 4). The median prednisone dose at baseline (start of the open-label prednisone taper period) was higher in the TCZ Q2W group (35 mg/day) than the other treatment groups (30 mg/day).

Table 4: Summary of GCA Disease Characteristics at Baseline (All Patients)

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=50)
Duration of GCA (days)				
n	50	51	100	50
Mean (SD)	364.66 (569.85)	255.22 (435.45)	306.80 (563.50)	258.38 (500.68)
Median	80.00	53.00	52.00	41.50
Min - Max	12.0 - 2698.0	8.0 - 1789.0	9.0 - 2856.0	13.0 - 2708.0
Disease Onset				
n	50	51	100	50
New Patient	23 (46.0%)	23 (45.1%)	47 (47.0%)	26 (52.0%)
Relapse Patient	27 (54.0%)	28 (54.9%)	53 (53.0%)	24 (48.0%)
Prednisone dose at baseline (mg/day)				
n	50	51	100	49
Mean (SD)	34.60 (12.97)	34.48 (14.20)	34.60 (13.37)	35.92 (13.76)
Median	30.00	30.00	30.00	35.00
Min - Max	20.0 - 60.0	5.0 - 60.0	10.0 - 60.0	5.0 - 60.0
Prednisone dose (<=30mg/day, >30mg/day)				
n	50	51	100	50
=<30 mg/day	27 (54.0%)	26 (51.0%)	52 (52.0%)	25 (50.0%)
>30 mg/day	23 (46.0%)	25 (49.0%)	48 (48.0%)	25 (50.0%)
First steroid for GCA (mg)				
n	50	50	100	49
Mean (SD)	104.74 (197.94)	61.76 (44.95)	79.02 (143.91)	78.40 (150.75)
Median	60.00	60.00	60.00	50.00
Min - Max	20.0 - 1000.0	10.0 - 250.0	2.0 - 1000.0	5.0 - 1000.0
Baseline C-reactive protein (CRP) (mg/L)				
n	50	51	100	49
Mean (SD)	7.69 (10.32)	8.17 (21.00)	6.78 (8.70)	11.36 (25.38)
Median	3.64	3.56	3.67	4.52
Min - Max	0.2 - 47.1	0.2 - 149.0	0.2 - 45.5	0.2 - 154.0
Baseline erythrocyte sedimentation rate (ESR) (mm/h)				
n	50	51	99	49
Mean (SD)	28.77 (25.43)	24.22 (18.19)	24.62 (18.66)	20.78 (18.13)
Median	23.00	20.00	19.00	15.00
Min - Max	1.0 - 115.0	2.0 - 75.0	2.0 - 95.0	0.0 - 79.0
Signs and Symptoms				
n	50	51	100	50
Both	20 (40.0%)	24 (47.1%)	37 (37.0%)	23 (46.0%)
Cranial Only	20 (40.0%)	16 (31.4%)	41 (41.0%)	18 (36.0%)
PMR Only	10 (20.0%)	11 (21.6%)	22 (22.0%)	9 (18.0%)

Source: Adapted from Clinical Study Report Table 12

As noted by the Applicant, the normal inflammatory markers at baseline are likely due to the use of 20-60 mg/day of steroids during the screening period. Patients in the TCZ Q2W had shorter duration of disease, lower ESR, higher CRP, and higher prednisone dose at baseline, reflecting potentially more aggressive initial therapy or a lower inflammatory burden. The small differences in baseline prednisone dose and the relatively small differences in median baseline inflammatory markers are unlikely to affect the results of this study that incorporated a blinded standardized prednisone taper.

Concomitant Medications

As defined in the protocol, all patients were treated with glucocorticoids. Patients could receive additional glucocorticoids for treatment of concomitant conditions; 32 patients received concomitant oral, intravenous or intramuscular steroids for indications other than GCA or PMR treatment (2.0% PBO+26 wk, 3.9% PBO+52 wk, 12.0% TCZ QW, 18.4% in TCZ Q2W based on this reviewer's analyses).

Seventy seven patients (30.7%) received treatment with lipid lowering agents, primarily statins (72 patients) during the treatment and follow-up periods. A minority of patients (2.4%) received ezetimibe, ezetimibe/simvastatin, or fibrates. Use of lipid lowering agents was generally balanced across the treatment groups (PBO+26 wk: 26.0%, PBO+52 wk: 33.3%, TCZ QW: 32.0%, and TCZ Q2W: 30.6%). Concomitant aspirin use was generally balanced as well (PBO+26 wk: 62.0%, PBO+52 wk: 56.9%, TCZ QW: 57.0%, and TCZ Q2W: 59.2%).

Bisphosphonate treatment was advised in the protocol for prevention of glucocorticoid-induced osteoporosis at the discretion of the investigator unless contraindicated. Osteoporosis was to be treated according to local practice. Bisphosphonate use was greater in the TCZ Q2W treatment group (59.2%) as compared to the other groups (TCZ QW: 47.0%, PBO+26 wk: 44.0%, and PBO+52 wk 47.1%). Six patients received concomitant denosumab (1 PBO+26 wk, 2 TCZ QW, and 3 TCZ Q2W), while 2 patients (1 PBO+26 wk, 1 TCZ QW) received teriparatide.

A slightly greater proportion of patients in the placebo treatment groups had prior or concomitant treatment with immunosuppression (Table 5). One patient (PBO+26 wk) previously received adalimumab, etanercept, and golimumab for treatment of spondyloarthropathy and 1 patient (TCZ QW) received etanercept for rheumatoid arthritis. In addition, 1 patient (TCZ QW) had a history of use of infliximab for GCA, and received concomitant infliximab after an AE of spondyloarthritis.

A minority of patients received concomitant immunosuppression during the study. Thirty five (13.9%) patients received concomitant methotrexate (8 PBO+26 wk, 10 PBO+52 wk, 11 TCZ QW, and 6 TCZ Q2W). One patient in the TCZ Q2W received concomitant IV cyclophosphamide treatment for an indication of 'arteritis axillaris,' during a hospitalization for GCA. One patient in the TCZ QW group received concomitant rituximab for GCA after discontinuing TCZ based on physician decision that GCA was resistant to treatment. In addition, 1 patient received concomitant topical tacrolimus for lichen sclerosus et atrophicus, and 1 patient each received concomitant ophthalmic cyclosporine for keratoconjunctivitis sicca and chronic dry syndrome.

Table 5: Concomitant Use of Immunosuppression (Safety Population)

	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Patients with prior or concomitant immunosuppression with:	12 (24.0)	13 (25.5)	20 (20.0)	10 (20.4)
Adalimumab	1 (2.0)	0	0	0
Azathioprine	2 (4.0)	3 (5.9)	2 (2.0)	1 (2.0)
Cyclosporine	0	1 (2.0)	1[1] (1.0)	1[1] (2.0)
Cyclophosphamide	3 (6.0)	1 (2.0)	1 (1.0)	1 (2.0)
Etanercept	1 (2.0)	0	1 (1.0)	0
Golimumab	1 (2.0)	0	0	0
Hydroxychloroquine	2[2] (4.0)	1[2] (2.0)	0	0
Infliximab	0	0	1 (1.0)	0
Leflunomide	2[3] (4.0)	2 (3.9)	1 (1.0)	0
Methotrexate	12 (24.0)	12 (23.5)	16 (16.0)	9 (18.4)
Mycophenolate Mofetil	1 (2.0)	0	0	0
Rituximab	0	0	1 (1.0)	0
Tacrolimus	0	1[4]	0	0

[1] Ciclosporin non GCA indications: Ophthalmic formulation for keratoconjunctivitis sicca (TCZ Q2W) and chronic dry eye syndrome (TCZ QW)
[2] Hydroxychloroquine non GCA indications: 1 Sjogren Syndrome (PBO+26 wk), 1 rheum polymyalgia (PBO+52 wk)
[3] Leflunomide non GCA indications: 1 Sjogren Syndrome or Rheumatoid Arthritis (PBO+26 wk)
[4] Tacrolimus non GCA indications: 1 lichen sclerosus et atrophicus
Reviewer JMP analysis ACM dataset using variables CMDECOD, CMINDC, CMTIREL, TRT01A, USUBJ

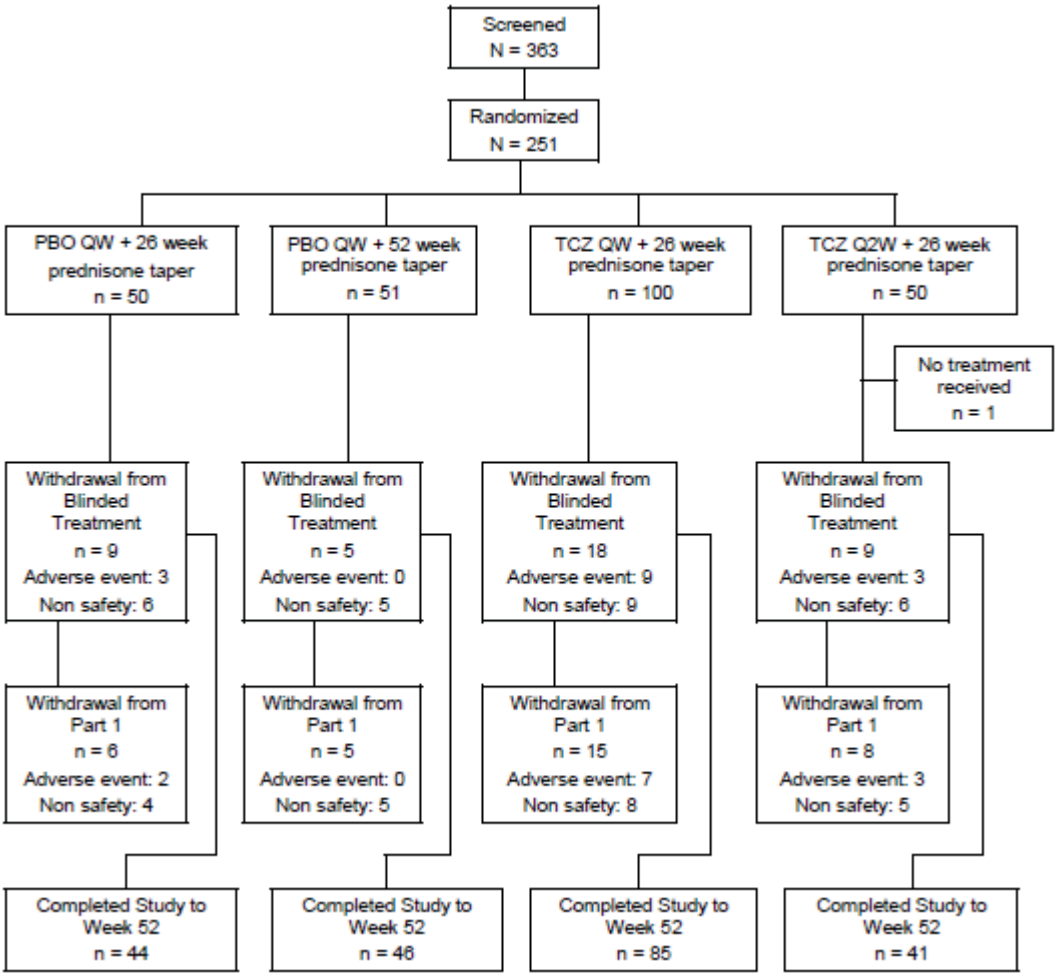
A greater proportion of patients in the TCZ Q2W treatment group received concomitant steroids for treatment of conditions other than GCA and PMR, while patients in the placebo treatment groups received less concomitant steroids for other conditions. Use of aspirin, which may decrease vascular events in patients with GCA, and use of lipid lowering therapies were generally similar across the treatment groups. Methotrexate was the most frequently used concomitant immunosuppressive agent and was used more frequently in the placebo groups than the TCZ groups. Other concomitant immunosuppression included 1 patient who received rituximab, 1 patient who received cyclophosphamide, and 1 patient who received infliximab. The balanced use of concomitant immunosuppression is unlikely to impact the efficacy results in the study. While the greater use of concomitant steroids in the TCZ Q2W could decrease disease activity in those patients, cumulative prednisone dose to Week 52 was a secondary endpoint and included use of systemic commercial prednisone for indications other than GCA. The median cumulative prednisone dose to Week 52 was lower in the TCZ treatment groups as compared to the placebo treatment groups. Therefore, the additional prednisone is unlikely to have impacted the results of the study.

6.1.3 Subject Disposition

Patients were enrolled at 76 active centers in 14 countries. Three hundred and sixty three (363) patients were screened and 251 patients were randomized as follows: 50 patients to placebo in combination with a 26-week prednisone taper, 51 patients to receive placebo in combination with a 52-week prednisone taper, 100 patients to receive TCZ QW in combination with a 26-week prednisone taper, and 50 patients to receive TCZ Q2W in combination with a 26-week prednisone taper. The main reasons for screen failure were failure to meet criteria for diagnosis of GCA (24 patients), inability or unwillingness to provide written informed consent (24 patients), absence of new-onset or relapsing active disease as defined in the protocol (10 patients), and ALT or AST levels outside the specified range (6 patients). One patient randomized to receive TCZ Q2W withdrew the day of randomization and did not receive study drug, and is therefore not included in the intention-to-treat or safety analysis populations.

Patients who withdrew from study treatment could remain in Part 1 of the study and continue on the blinded prednisone taper; patients could also withdraw from Part 1 any time prior to Week 52 but remain in the study for safety follow-up visits. During the 52-week double-blind period, 41 patients discontinued blinded treatment (TCZ/placebo/prednisone): 9 patients (18%) in the PBO+26 wk group, 5 patients (10%) in the PBO+52 wk group, 18 patients (18%) in the TCZ QW group, and 9 patients (18%) in the TCZ Q2W group (Figure 4).

Figure 4: Patient disposition



Source: Clinical Study Report Figure 2

The most frequently reported reasons for discontinuation from double-blind treatment (TCZ/placebo/prednisone), were adverse events (9 patients in TCZ QW, 3 patients each in PBO+26 wk and TCZ Q2W), and withdrawal by patient (5 patients TCZ QW, 2 patients each PBO+26wk and TCZ Q2W, and 1 patient in PBO+52wk) (Table 6). Two additional patients in each of the TCZ QW and TCZ Q2W groups were withdrawn from blinded study treatment due to an AE; however, these were attributed on the CRF to other and withdrawal by subject (TCZ QW), and withdrawal due to physician decision and withdrawal due to lack of efficacy (TCZ Q2W).

Of the 41 patients who discontinued double-blind treatment, 34 patients withdrew from Part 1 of the study. Note, patient 255211/10402 was identified as discontinuing double blind treatment, but both not discontinuing and not completing Part 1. The patient was lost to follow-up. In response to an information request dated 08Feb2017, the Applicant explains that as this patient did not discontinue Part 1 (DISCP1='N'), therefore the number of patients completing the study to Week 52, calculated as the total number of treated patients in the treatment group minus the number of treated patients

discontinuing Part 1, is the 49 TCZ Q2W treated patients – 8 patients who discontinued Part 1 = 41 patients in the TCZ Q2W who completed the study to Week 52.

Table 6: Patient Disposition, Part 1

	Not treated N = 1 n (%)	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Deaths	0	0	0	0	0
Completed study to Week 52	0	44 (88.0)	46 (90.2)	85 (85.0)	41 (81.6)
Completed blinded treatment	0	41 (82.0)	46 (90.2)	82 (82.0)	40 (80.0)
Discontinued blinded study treatment[1]	1 (100.0)	9 (18.0)	5 (10.0)	18 (18.0)	9 (18.0)
Reasons for discontinuation from blinded treatment					
Adverse event	0	3 (6.0)	0	9 (9.0)	3 (6.0)
Lack of efficacy	0	1 (2.0)	2 (3.9)	1 (1.0)	3 (6.0)
Non-compliance	0	0	0	1 (1.0)	0
Other	1 (100.0)	0	0	1 (1.0)	0
Physician decision	0	3 (6.0)	1 (2.0)	1 (1.0)	1 (2.0)
Protocol violation	0	0	1 (2.0)	0	0
Withdrawal by subject	0	2 (4.0)	1 (2.0)	5 (5.0)	2 (4.0)
Discontinued Part 1	1 (100.0)	6 (12.0)	5 (10.0)	15 (15.0)	8 (16.0)
Reasons for discontinuation from Part 1					
Adverse event	0	2 (4.0)	0	7 (7.0)	3 (6.0)
Lack of efficacy	0	2 (4.0)	2 (3.9)	1 (1.0)	3 (6.0)
Non-compliance	0	0	0	1 (1.0)	0
Other	1 (100.0)	0	0	0	0
Physician decision	0	0	1 (2.0)	0	0
Protocol violation	0	0	1 (2.0)	0	0
Withdrawal by subject	0	2 (4.0)	1 (2.0)	6 (6.0)	2 (4.0)

[1]TCZ/placebo/prednisone
Source: Adapted from Applicant CSR Table 6, Table 7
Reviewer JMP Analysis: ASL dataset, using terms DISCDBR, ACTARM, DISCSTUD, DISCP1, DISCP1R, COMPTRT

The most common reasons for premature discontinuation from Part 1 of the study were due to adverse event (7 patients in TCZ QW group, 3 patients in TCZ Q2W, and 2 patients in PBO+26 wk groups) and withdrawal by subject (6 patients in TCZ QW, 2 patients each in TCZ Q2W and PBO+26wk groups, and 1 patient in PBO+52 wk) as shown in Table 6. The Applicant provided a review of the reasons for withdrawal of consent by the subject; no pattern of withdrawal was observed. Five patients withdrew after flare (2 in PBO+26wk, 2 in TCZ QW, and 1 in TCZ Q2W) and withdrew consent for the following reasons: they wanted to know their prednisone dose (1), they declined

escape prednisone (2), desire to try additional therapies (1), and did not wish to travel to study visits (1). Reviewer analysis of the reported terms for patients who discontinued double blind treatment due to physician decision include serious elevated liver enzymes (1 PBO+52 wk), lack of efficacy or GCA flare (1 PBO+26 wk, 1 TCZ Q2W, 1 TCZ QW), physician decision prior to hip prosthesis placement (1 PBO+26 wk), and AE [of erysipelas] (1 PBO+26 wk). One patient in the TCZ QW group discontinued blinded treatment for reason of physician decision, later discontinued Part 1 for adverse event, but subsequently discontinued the study for reason of physician decision. Some patients who discontinued double blind treatment for reasons attributed to physician decision, may have been more accurately attributed to other reasons of discontinuation, such as lack of efficacy or adverse event, however these few patients, generally balanced across the treatment groups, would not influence the overall assessment of safety or efficacy.

Eighty eight patients completed up to study week 100 and were included in the Part 2 data cut. Of the 88 patients, 33 patients received TCZ QW, 17 patients received TCZ Q2W, 18 patients received PBO+26 wk, and 20 patients received PBO+52 wk in Part 1. Of the 38 patients who received placebo in Part 1, 18 patients (47.4%) received open-label TCZ at Week 52. Of the 50 patients who received TCZ in Part 1, 27 patients (14 TCZ QW, 13 TCZ Q2W) received open label TCZ at Week 52, based on this reviewer's analysis. One patient (PBO+26 wk), not receiving OL TCZ, withdrew consent and discontinued Part 2 of the study.

Protocol Violations

There was one major study conduct protocol deviation leading to discontinuation in a patient enrolled in the study in the PBO+52 wk treatment group with PMR (rather than GCA with PMR symptoms) and subsequently withdrawn from the study by the Applicant. Fifteen patients did not meet the eligibility criteria (PBO+26 wk: 4, PBO+52 wk: 1, TCZ QW: 4, TCZ Q2W: 6). Eligibility criteria violations included the following inclusion and exclusion criteria: available historical ESR ≥50 mm/hr, randomization within 6 weeks of baseline visit, exclusion of patients who received >100 mg daily IV methylprednisolone within 6 weeks of baseline, exclusion of patients with active infections, TB screening requirements, and exclusion of patients with absolute lymphocyte count $<0.5 \times 10^9$/L.

Five patients received an incorrect dose of prednisone at baseline in error. Three of these were considered major protocol deviations, although the patients remained in the study: 1 patient in the PBO+52 wk group took only a single capsule (5 mg/day) during Week 1 of the study, 1 patient in the TCZ Q2W group started the open-label prednisone taper period on a dose of 5 mg/day, and 1 patient in the TCZ QW group did not take open-label prednisone and started on blinded treatment (15 mg/day) during Week 1. Two additional patients had dosing errors at baseline that were not considered protocol violations: 1 patient in the PBO+52 wk group took 28.5 mg/day prednisone and 1 patient in the TCZ QW group took 10 mg/day prednisone.

Additional protocol violations are listed below:

Table 7: Additional Protocol Violations

High Level Category	Low Level Category	Number of Occurrences
Informed Consent	Delay in signing updated ICF	28
	RCR-Genetic sample collected without signed consent	16
	Translation procedures not followed	1
	Outdated version of ICF signed	1
Blinded TCZ	Incorrect syringe used	10
	2 hour observation after injection not conducted	6
	First 4 injections not performed in hospital	1
	Incorrect storage conditions	1
	Injection procedure not followed	1
Blinded Prednisone Taper	Incorrect medication pack dispensed	1
Escape Prednisone	Starting dose too low	6
	Delay in starting treatment	2
	Expired medication used	1
	Dispensed incorrect medication pack	1
OL TCZ	Received OL TCZ while in remission	2
	Expired TCZ used	1
	Injection less than 5 days since previous injection (minor violation)	1
Dual Assessor	Incorrect person performed task	34
	GCA assessment procedure not followed	3
Prohibited Treatment	Parenteral steroids	8
Study Procedure	Additional visit recommended by local EC not done	1
Laboratory Assessments	Unblinded CRP	6
	Risk mitigation guidance not followed	1

Source: Adapted from Applicant Response to IR dated 31Jan2017, Table 3

Three patients received > 100 mg daily IV methylprednisolone within 6 weeks of baseline, 1 each in the TCZ QW, TCZ Q2W, and PBO+26 wk treatment groups. One patient in the TCZ QW group and one in the PBO+26wk had a historical ESR <50 mm/hr and one patient in the TCZ Q2W group had no documented historical ESR values. Previous treatment with high dose corticosteroids and a lower inflammatory burden at baseline, could bias the results, however given that these occurred in equal and small numbers in 3 of the treatment groups, it is unlikely to have an impact in the primary endpoint comparing the TCZ treatment groups to the PBO+26 wk group.

Study treatment was to be unblinded for all unexpected SAEs that were considered related to study drug by the investigator. Following unblinding, the decision to withdraw the patient was at investigator discretion. As detailed in the iDMC meeting minutes, 4 patients were unblinded by sites and 3 by Roche Drug Safety. Reasons for code breaks include SAEs and 1 code break due to lack of efficacy.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint, the proportion of patients achieving sustained remission from Week 12 through Week 52, is a composite endpoint defined by: (1) absence of flare following induction of remission by Week 12 and where flare is defined as the recurrence of signs or symptoms of GCA and/or ESR ≥30 mm/hr attributable to GCA, (2) normalization of CRP (<1 mg/dL), (3) successful prednisone tapering, and (4) remaining in the study through 52 weeks. Patients who received >100 mg of additional glucocorticoid dosing from Week 12 to Week 52 were considered as not adhering to the prednisone taper regimen.

Remission at Week 12 was achieved by 83.0% of patients in the TCZ QW group, 81.6% in the TCZ Q2W group, 49.0% in the PBO+52 wk, and 42.0% in the PBO+26 wk group. As shown in Table 8, a significantly greater proportion of patients in the TCZ QW (56 patients, 56.0%) and the TCZ Q2W (26 patients, 53.1%) achieved sustained remission as compared to the PBO+26 wk treatment group (7 patients, 14.0%) at Week 52. The differences in response rates between the TCZ groups and PBO+26 wk group (42.0% for TCZ QW and 39.1% for TCZ Q2W) was statistically significant (p value <0.0001) for both comparisons. As TCZ can lower inflammatory markers, such as ESR and CRP, based on its mechanism of action, a sensitivity analysis was conducted where the primary analysis was repeated on the basis of only signs and symptoms of disease excluding the requirement for normalization of CRP from the definition of remission; this analysis was consistent with the primary analysis for both TCZ dose groups. To evaluate the effect of missing data on the results, tipping point analyses were conducted where all non-responders with missing data were considered responders, and where all missing PBO+26 wk considered responders and missing non-responders in TCZ groups remained non-responders. Other sensitivity analyses conducted by the Applicant included an analysis of completers adhering to blinded TCZ/placebo study medication and analysis irrespective of adherence to the prednisone taper regimen. These sensitivity analyses were supportive of the primary analysis. The FDA statistical reviewer conducted additional sensitivity analyses to assess responders in the absence of elevation in ESR, in the absence of signs or symptoms of GCA and/or elevation in ESR, normalization of CRP only, and successful prednisone tapering. These analyses removed the dependence on acute phase reactants from the definition of sustained remission to evaluate each component's contribution to the definition of sustained remission. These analyses were also supportive of the primary analysis. In the analysis of responders based only on absence of signs and symptoms of GCA regardless of acute phase reactants, regardless of prednisone taper, and regardless of escape, the proportion of responders was consistently numerically greater in both TCZ treatment groups as compared to the PBO+26 wk group, reaching statistical significance for the TCZ QW comparison.

Table 8: Proportion of Patients Achieving Sustained Remission at Week 52 (TCZ vs. PBO+26 wk), Primary Endpoint

	PBO+26wk N = 50 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Protocol-defined sustained remission	7 (14.0)	56 (56.0)	26 (53.1)
Difference in response rates (99.5% CI)		42.0%; (18.0, 66.0)	39.1% (12.5, 65.7)
p-value		<0.0001	<0.0001
Individual components of sustained remission:			
Absence of signs or symptoms of GCA only	20 (40.0)	69 (69.0)	28 (57.1)*
Diff; 99.5% CI		29.0%; (5.1, 52.9)	17.1%; (-11.1, 45.3)
p-value		0.00073	0.09678
Absence of ESR ≥30 mm/hr attributable to GCA only	20 (40.0)	83 (83.0)	37 (75.5)*
Diff; 99.5% CI		43.0%; (20.4, 65.6)	35.5%; (7.6, 63.4)
p-value		<0.0001	0.00045
Normalization of CRP only	17 (34.0)	72 (72.0)	34 (69.4)*
Diff; 99.5% CI		38.0%; (14.1, 61.9)	35.4%; (7.2, 63.6)
p-value		<0.0001	0.00052
Successful prednisone tapering only	10 (20.0)	60 (60.0)	28 (57.1)
Diff; 99.5% CI		40.0%; (15.7, 64.3)	37.1%; (9.7, 64.6);
p-value		<0.0001	0.00018

*Additional patient lost to follow-up considered non-responder in FDA analysis
Source: Analysis by FDA Statistical Reviewer Dr. Koh

Table 9 presents a subgroup analysis of the proportions of patients who did not meet the components of the definition of sustained remission, and were therefore non-responders in the analysis of the primary endpoint. A greater proportion of patients in the placebo groups received escape prednisone, experienced first flares based on both signs and symptoms and/or elevated ESR, and had two consecutive elevated CRP values without flare as compared to the TCZ treatment groups. The majority of flares were due to clinical signs and symptoms of GCA, while 9 first flares (8 in placebo groups, 1 in TCZ QW) were reported due to elevation of ESR without signs or symptoms. Given the pharmacodynamic effect of TCZ on inflammatory markers, it is not unexpected that fewer patients in the TCZ treatment groups had elevations in ESR and CRP. For 15 patients, CRP elevations were the only components of the remission definition not met. Sensitivity analysis in which these 15 patients were classified as responders, still showed superiority of the two TCZ doses over PBO+26 wk. Additional prednisone >100 mg from Week 12 to Week 52 (including all escape therapy, commercial prednisone, and taper prednisone) was received by 3 patients in the TCZ QW group who did not receive escape prednisone, while 1 patient in each of the

placebo groups received escape prednisone but received <100 mg of total additional prednisone. A sensitivity analysis that considered the 3 patients with >100 mg additional prednisone as non-responders (i.e., excluding adherence to the protocol-defined prednisone taper regimen) still showed superiority of the two TCZ doses over PBO+26 wk group. A greater proportion of patients in the placebo treatment groups were considered non-responders due to use of escape prednisone, first flares based on signs and symptoms and ESR elevation, first flare with ESR elevation only, elevated CRP without flare at Week 12 or later, and non-adherence to the prednisone taper regimen (use of additional prednisone exceeding 100 mg).

Table 9: Summary of Non-responders

	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Received escape prednisone	37 (74.0)	28 (54.9)	23 (23.0)	16 (32.7)
First flare of any type	36 (72.0)	29 (56.9)	27 (27.0)	17 (34.7)
First flare of SnS and ESR elevation	19 (38.0)	19 (37.3)	0	3 (6.1)
First flare with SnS only	11 (22.0)	8 (15.7)	25 (25.0)	14 (28.6)
First flare with ESR elevation only	6 (12.0)	2 (3.9)	1 (1.0)	0
Withdrawal from study prior to Week 52	6 (12.0)	5 (9.8)	15 (15.0)	8 (16.3)
Elevated CRP without flare at Wk 12 or later	26 (52.0)	31 (60.8)	5 (5.0)	3 (6.1)
Received additional prednisone, including escape, (>100 mg)	36 (72.0)	27 (52.9)	26 (26.0)	16 (32.7)

SnS = Signs and Symptoms
Source: Adapted from Clinical Study Report Table 18

6.1.5 Analysis of Secondary Endpoints(s)

Key Secondary Endpoint

The key secondary endpoint was the proportion of patients in sustained remission at Week 52 in the TCZ groups as compared with the placebo+52 week prednisone taper regimen. Sustained remission at Week 52 was achieved by 56.0% of patients in the TCZ QW group and 53.1% of patients in the TCZ Q2W group, as compared to 17.6% in the PBO+52 wk group (Table 10). The criteria for non-inferiority whereby the lower bound of the 99.5% confidence intervals for both TCZ dose groups was ≥ -22.5% was met for both TCZ treatment groups. The non-inferiority margin was selected to preserve at least 50% of a minimum treatment effect of 45% observed with corticosteroid treatment alone. In comments communicated 10June2016, the Agency questioned the

utility of a non-inferiority assessment as this would not be necessary to establish efficacy, which would be provided by the planned superiority assessment of the primary endpoint. The Agency recommended that unless adequate justification of why ruling out losses in efficacy greater than a specific non-inferiority margin would provide useful information to patients and prescribers, the secondary endpoint should assess whether TCZ plus 26 week steroid taper is superior to the placebo plus 52 week steroid taper treatment group. Therefore, the non-inferiority assessment will not be addressed further and the superiority assessment will be discussed below.

The subsequent superiority analysis demonstrated statistically significant differences in sustained remission rates in each of the TCZ groups as compared to the PBO+52 wk group, with a p-value of <0.0001 for the comparisons with TCZ QW and a p-value of 0.0002 for the TCZ Q2W comparison (Table 10).

Table 10: Proportion of Patients Achieving Sustained Remission at Week 52 (TCZ vs. PBO+52 wk), Key Secondary Endpoint

	PBO+52 wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Protocol-defined sustained remission	9 (17.6)	56 (56.0)	26 (53.1)
Difference in response rates (99.5% CI)		38.4; (14.4, 62.3)	35.5; (8.6, 62.2)
p-value		< 0.0001	0.00024
Individual components of sustained remission:			
Absence of signs or symptoms of GCA only	23 (45.1)	69 (69.0)	28 (57.1)*
Diff; 99.5% CI		23.9; (0.3, 47.5)	12.0; (-16.0, 40.1)
p-value		0.00465	0.23448
Absence of ESR ≥ 30 mm/hr attributable to GCA only	22 (43.1)	83 (83.0)	37 (75.5)*
Diff; 99.5% CI		39.9; (17.6 , 62.1)	32.4; (4.8, 60.0)
p-value		<0.0001	0.00098
Normalization of CRP only	13 (25.5)	72 (72.0)	34 (69.4)*
Diff; 99.5% CI		46.5; (22.6, 70.5)	43.9; (15.9, 71.9)
p-value		<0.0001	<0.0001
Successful prednisone tapering only	20 (39.2)	60 (60.0)	28 (57.1)
Diff; 99.5% CI		20.8; (-3.3, 44.9)	17.9; (-10.1, 46.0)
p-value		0.01596	0.07418

*Additional patient lost to follow-up considered non-responder in FDA analysis
Source: Analysis by Statistical Reviewer Dr. Koh

Similar sensitivity analyses to those discussed above for the primary endpoint were performed for the key secondary endpoint, and were generally consistent with the results for the ITT population. In an analysis of responders based on signs and symptoms of disease, excluding the requirement for normalized CRP, both TCZ QW and TCZ Q2W were superior to PBO+52 wk, with the TCZ QW comparison reaching statistical significance. In an analysis conducted by the FDA statistical reviewer, the number of responders in the TCZ groups was similar when evaluating remission based on absence of flares where flares are defined by signs and symptoms of GCA only, as compared to where the definition of flare includes ESR ≥30 attributable to GCA, whereas the number of responders in the placebo group is higher when flares are defined by signs and symptoms of GCA only. Importantly, these analyses were not controlled for multiplicity.

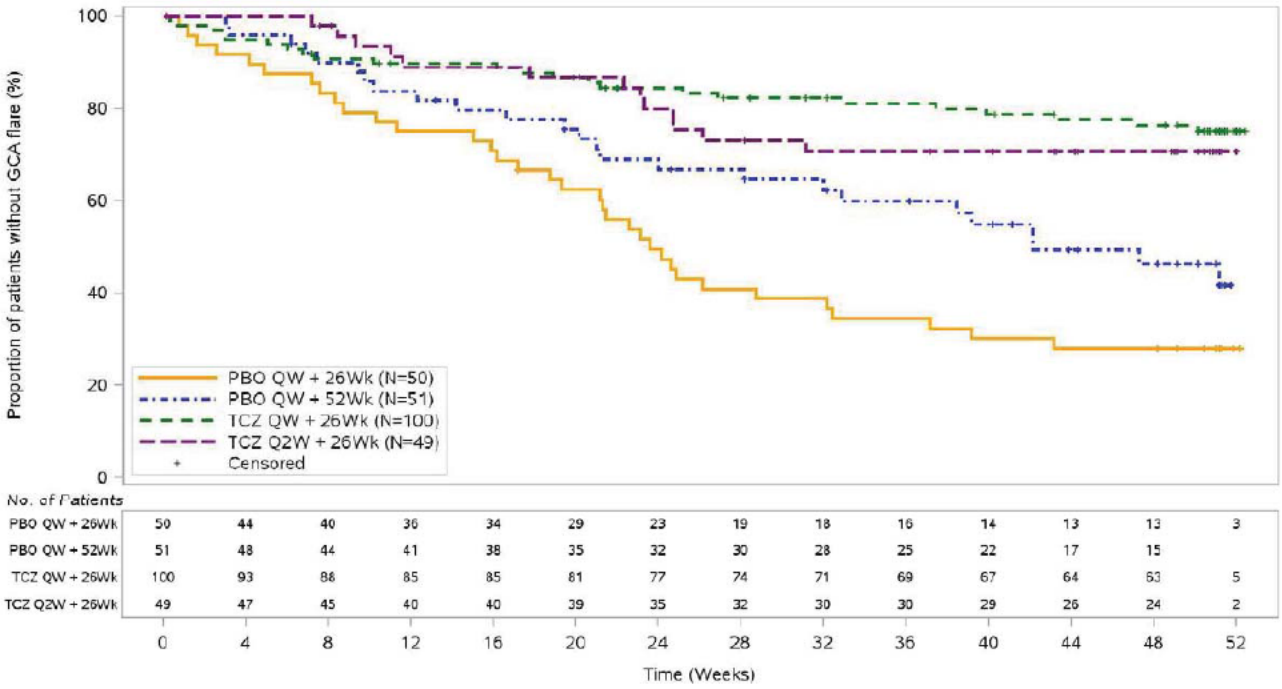
A greater proportion of patients achieved the composite endpoint of sustained remission from Week 12 to Week 52 with adherence to protocol-defined steroid taper, in both TCZ treatment groups as compared to the PBO+52 wk steroid taper. This is the comparison most relevant to clinical practice where patients are often treated with a prolonged steroid taper over one year or longer. The superiority of treatment with TCZ QW and TCZ Q2W was supported by various sensitivity analyses examining the individual components of the composite endpoint. These sensitivity analyses were generally consistent with the primary analysis. In these analyses, only TCZ QW remained statistically significantly superior to PBO+52 wk when analysis excluded the requirement for normalization of CRP and analysis of remission based on absence of flare, where flare is defined based on signs or symptoms of GCA only.

Other Secondary Endpoints

Time to First GCA Flare

Disease flares were determined by the investigator and based on the recurrence of signs or symptoms of GCA and/or ESR ≥30 mm/hr attributable to GCA. The median time to first GCA flare following remission was 165 days in the PBO+26 wk group and 295 days in the PBO+52 wk group. Fewer than 50% of patients in the TCZ QW and TCZ Q2W group (23% and 26.5% respectively) experienced a disease flare by Week 52, and therefore median time to flare was not calculable. A Kaplan-Meier plot of time to first GCA flare shows separation of the placebo treatment groups from the TCZ treatment groups in Figure 5. Time to event analysis of the hazard ratios, accounting for stratification at baseline, for TCZ vs. PBO+26 wk were 0.23 (99% CI: 0.11 to 0.46; p<0.0001) for the TCZ QW group and 0.28 (99% CI: 0.12 to 0.66; p<0.0001) for the TCZ Q2W group, consistent with a lower risk of flare after induction of remission in patients in the TCZ treatment groups as compared to the placebo groups. In an analysis comparing the TCZ treatment groups to the PBO+52 wk taper regimen, the hazard ratio was 0.39 (99% CI: 0.18 to 0.82; p=0.0011) for the TCZ QW group, while the hazard ratio was 0.48 (99% CI: 0.20 to 1.16; p=0.0316) for the TCZ Q2W group which did not meet the pre-specified significance threshold of p<0.01.

Figure 5: Kaplan-Meier Plot of Time to First GCA Disease Flare (ITT Population)



Patients who were never in remission are censored at Day 1.
Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.

Source: Clinical Study Report Figure 4

While the Applicant emphasized the importance of these results, the time to first flare analysis was performed only in patients who achieved remission by Week 12 and these comparisons are based on a post-randomization variable (whether a patient is in remission) rather than on the original randomization. In these analyses, the hazard ratios showed decreased risk of flares with both TCZ dose groups in comparison to both placebo treatment groups, however the comparison of TCZ Q2W to PBO+52 wk was not statistically significant. However, this assessment is confounded by potential differences in patient and disease characteristics between patients who achieve remission and those that do not. This is no longer a randomized population, limiting conclusions that may be drawn for treatment of patients who are not in remission. Thus, this analysis does not preserve the integrity of randomization (b) (4)

Through Week 52, 109 patients experienced a flare. Greater proportions of patients reported a flare in the PBO+26 wk (72.0%) and PBO+52 wk (56.9%) as compared to the TCZ QW (27.0%) and TCZ Q2W (34.7%) treatment groups (Table 11). A similar proportion of patients experienced flares with signs and symptoms of GCA across the treatment groups. The most frequently reported signs and symptoms at the time of flare were cranial signs and symptoms of GCA (see comment below) and symptoms of PMR, and the proportions of patients experiencing these symptoms were generally similar across the treatment groups. Few patients had fever or visual symptoms. The

patients with unilateral and bilateral blindness had ongoing symptoms from baseline. The most frequent reported terms listed under “other signs and symptoms” include fatigue, night sweats, and dizziness. Other reported symptoms include headache, jaw pain, PMR/myalgia, and joint pains.

The evaluation of clinical signs and symptoms to be conducted at every study visit are listed in section 5.3 above. The Clinical Study Report refers to the patients who have “Signs or symptoms of GCA” as having cranial signs or symptoms of GCA, however the cranial specification is not included in the electronic case report form (eCRF) and it is not clear that investigators would have consistently chosen this only for cranial signs or symptoms of GCA. Therefore, this may include a broader range of signs or symptoms of GCA. Fever, symptoms of PMR, and the listed visual symptoms in Table 11 are listed separately on the eCRF. Whether flares were due to cranial symptoms of GCA or other symptoms of GCA as determined by the investigator does not impact the interpretation of the efficacy results of the study.

As may be expected based on the pharmacodynamic effect of TCZ, more patients had an elevated ESR attributable to GCA in the placebo treatment groups as compared to the TCZ groups, in those patients who experienced a flare, as well as in the overall patient population. Flares due to elevated ESR attributable to GCA in the absence of signs and symptoms occurred in 10 patients. The majority of patients who flared received escape prednisone therapy (93.6%) with the exception of 7 patients (1 PBO+52 wk, 2 TCZ Q2W, and 4 TCZ QW) who flared but did not receive escape prednisone. Note, as flares were based on the opinion on the investigator, patients could experience signs and symptoms of GCA and/or an elevated ESR attributable to GCA and still be considered in remission if the investigator did not determine that the symptoms were severe enough to be considered a flare. Flares were also reported for 2 patients who did not have clinical signs and symptoms of GCA or an elevated ESR attributed to GCA at that visit; 1 patient (TCZ QW) subsequently presented with amaurosis fugax and blurred vision at Week 3 and 1 patient (PBO+52 wk) whose escape prednisone was increased prior to Week 48 visit.

As discussed above, a greater proportion of patients in the placebo treatment groups as compared to the TCZ groups experienced flares. The clinical manifestations of flares (i.e., GCA signs and symptoms) were generally balanced across the groups, except for the greater proportions of patients reporting “other” signs and symptoms in the placebo groups. Consistent with the pharmacodynamic effect of TCZ on ESR, a greater proportion of patients in the placebo groups experienced flares associated with elevated ESR attributable to GCA or flares due to elevated ESR in the absence of signs and symptoms.

Table 11: Summary of Flares through Week 52 (ITT Population)

	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Patients who experienced flares	**36 (72.0)**	**29 (56.9)**	**27 (27.0)**	**17 (34.7)**
Flare Patients with ESR ≥30 mm/hr attributable to GCA	**27 (75.0)**	**21 (72.4)**	**1 (3.7)**	**3 (17.6)**
Signs and Symptoms of Flare, n (% of flare patients)	**32 (88.9)**	**29 (100.0)**	**25 (92.6)**	**17 (100.0)**
Fever	2 (5.6)	1 (3.4)	1 (3.7)	0
Signs or symptoms of GCA	25 (69.4)	20 (69.0)	18 (66.7)	13 (76.5)
Symptoms of PMR	20 (55.6)	16 (55.2)	17 (63.0)	9 (52.9)
Unilateral Blindness	1 (2.8)	0	0	0
Bilateral Blindness	0	0	0	1 (5.9)
Ischemic Optic Neuropathy	0	0	0	1 (5.9)
Amaurosis Fugax	1 (2.8)	0	0	1 (5.9)
Blurred vision	2 (5.6)	4 (13.8)	0	1 (5.9)
Diplopia	1 (2.8)	1 (3.4)	0	0
Other	14 (38.9)	15 (51.7)	7 (25.9)	4 (23.5)
Flares due to elevated ESR in absence of signs and symptoms, n (% of flare patients)	7 (19.4)	2 (6.9)	1 (3.7)	0

Source: Adapted from Clinical Study Report Table 25

Cumulative prednisone

Expected cumulative prednisone dose to Week 52 was calculated based on a patient's starting prednisone dose, the taper schedule, and the assumption that the patient continued the taper without error. Therefore, the expected prednisone dose is similar across the PBO+26 wk, TCZ QW, and TCZ Q2W as all specified a 26 week prednisone taper, while the expected dose is higher in the PBO+52 wk group which utilized a longer taper regimen. The median cumulative prednisone taper dose is similar in each of the treatment groups with a 26 week prednisone taper, while as predicted, the cumulative taper dose is higher in the PBO+52 wk group, as shown in Table 12. Overall, 104 patients were treated with escape prednisone; a greater proportion of patients in the placebo treatment groups received escape therapy and at higher median doses than in the TCZ groups (Table 12).

Median cumulative prednisone dose to Week 52 up to last follow-up including all taper prednisone (open-label and blinded taper), escape therapy, and commercial prednisone (via oral, intravenous, intramuscular, intra-arterial, subcutaneous, and 'other') was 1862.0 mg in each of the TCZ treatment groups, as compared with 3296.0 mg in the PBO+26 wk group and 3817.5 mg in the PBO+52 mg group. The mean cumulative dose was higher in the TCZ Q2W (2447.0 mg) than in the TCZ QW (2097.8 mg), likely due to the high doses of escape and/or commercial prednisone for some patients in the TCZ Q2W treatment group (Table 12). A greater proportion of patients in the placebo groups (PBO+26 wk: 72.0%, PBO+52 wk 52.9%) received greater than 100 mg of corticosteroids in excess of the specified taper regimen as compared to the TCZ QW (26.0%) and TCZ Q2W (32.7%) treatment groups. Patients who discontinued from the study prior to Week 52 are not included in the cumulative prednisone analysis. The FDA statistical reviewer conducted analyses adjusted for duration of study follow-up. The adjusted annual cumulative prednisone doses were highest in the placebo groups and lower in the TCZ treatment groups, as shown in Table 12, further supporting the decreased use of steroids in the TCZ treatment groups.

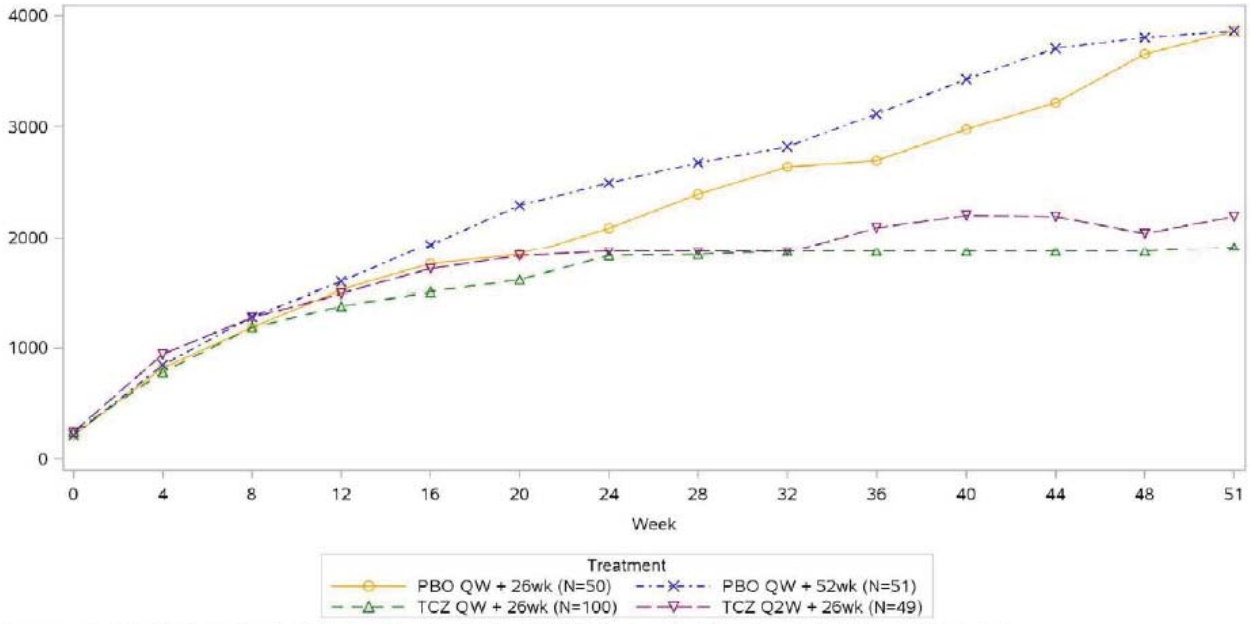
Table 12: Summary of Cumulative Prednisone Use to Week 52

	PBO+26wk N = 50	PBO+52wk N = 51	TCZ QW N = 100	TCZ Q2W N = 49
Median cumulative prednisone, mg	3296.0	3817.5	1862.0	1862.0
Mean cumulative prednisone , mg	3765.2	4199.0	2097.8	2447.0
Median cumulative prednisone taper, mg	1323.0	2205.0	1351.5	1345.0
Patients receiving escape prednisone, n (%)	37 (74.0)	28 (54.9)	23 (23.0)	16 (32.7)
Median escape prednisone, mg	2876.0	3643.8	2270.0	1990.3
Patients receiving >100 mg additional corticosteroids, n (%)	36 (72.0)	27 (52.9)	26 (26.0)	16 (32.7)
Median annual cumulative prednisone, mg	3804	3902	1887	2207

Source: Adapted from Clinical Study Report Table 18, Table 28, page 516.
Reviewer JMP analysis AEX dataset using terms EXTCATT, EXTDOST, TRT01P, USUBJID
ABASE dataset using terms P100FL, TRT01P
FDA Statistical Reviewer Dr. Koh

Figure 6 plots the cumulative prednisone dose over time by visit and treatment group. The curves were similar in the TCZ and placebo treatment groups up to approximately Week 16. Based on the protocol defined 26 week prednisone taper, the blinded taper regimen reaches 0 by approximately Week 27 for a starting prednisone dose of 60 mg/day, or earlier for starting doses less than 60 mg/day (Appendix 1). The curves of the TCZ groups plateau after Weeks 20-24, while the curves in the placebo groups continue to increase, reflecting the longer taper regimen of the PBO+52 wk group and the increased use of escape prednisone in the placebo groups.

Figure 6: Plot of Median Cumulative Prednisone Dose by Visit and Treatment Group to Week 52 (ITT Population)



For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) will be assumed to be the minimum dose tablet(s) available from that pack.
Patients who received increased prednisone due to entering escape therapy will be included in their original treatment group.
Patients who withdraw are excluded from the summaries for subsequent visits.
Prednisone records are reported up to study day 364. Week 0 to Week 51 includes the 52 weeks of Part 1 prednisone exposure.

Source: Clinical Study Report Figure 5

These analyses suggest that fewer patients in the TCZ treatment groups received escape prednisone and median cumulative prednisone use, including commercial prednisone patients may have received for other indications, was lower in these groups. The median cumulative prednisone use was the same between the TCZ Q2W and TCZ QW groups, however the mean prednisone use was greater in the TCZ Q2W group. In addition, numerically fewer patients in the TCZ QW group required escape prednisone. However, interpretation of the cumulative prednisone dose is limited in that patients who withdrew from the study are not included and a greater proportion of patients in the TCZ treatment groups withdrew from the study. Therefore, the cumulative prednisone dose in the TCZ treatment groups may have been greater than that reflected in Figure 6. Despite these limitations, the results are consistent with the totality of the data and supportive of a clinical benefit of TCZ in GCA.

Patient Reported Outcomes

The Applicant has submitted data on patient reported outcomes such as SF-36 and FACIT-F in support of this application. Of note, these endpoints are not disease-specific and their relevance in assessing clinical benefit in GCA is unclear. However, they are reviewed for completeness.

Change from baseline to Week 52 in SF-36 (Version 2) Physical Component Scores and Mental Component Scores were specified secondary endpoints, analyzed using a maximum likelihood-based repeated measures model, and estimates (least-square

means (LSM)) based on the regression model were reported. A numerical improvement in SF-36 MCS was observed between baseline and Week 52 in all treatment groups, while a numeric improvement in PCS was seen in only the TCZ treatment groups with a slight worsening in PCS score in the placebo groups (Table 13). Mean change from baseline to Week 52 was generally small across the treatment groups for each domain.

The patient global VAS was a specified secondary endpoint analyzed using a maximum likelihood-based repeated measures model. At Week 52, all treatment groups had a decrease in the patient global VAS scores, consistent with an improvement in patients' assessment of the effect of their GCA (Table 13). A numerically greater decrease was observed in the tocilizumab groups as compared to the placebo treatment groups.

Other quality of life outcome measures include change from baseline in FACIT-Fatigue score at Week 52 and change from baseline in EuroQol 5D score at Week 52. Numerically higher mean changes from baseline in the FACIT-Fatigue scores at Week 52 were observed in the TCZ treatment groups as compared with the placebo groups, indicating numerically greater improvement in the TCZ treatment groups. EQ-5D scores were generally stable at Week 52 across the treatment groups.

Table 13: Summary of Patient Reported Outcomes, Change from baseline to Week 52 (ITT population)

	PBO+26wk N = 50	PBO+52wk N = 51	TCZ QW N = 100	TCZ Q2W N = 49
SF-36				
N	41	43	82	39
LSM Change from baseline to Week 52 in PCS	-1	-0.4	4.2	2.3
LSM Change from baseline to Week 52 in MCS	5.3	1.9	8.1	6.6
VAS				
N	44	43	85	40
LSM Change from baseline to Week 52, Patient Global VAS	-7.2	-7.6	-17.1	-22
FACIT-Fatigue				
N	44	44	83	40
Mean change from baseline to Week 52, (standard deviation)	-0.27 (9.2)	1.44 (10.0)	5.38 (10.0)	3.92 (8.4)
EQ-5D				
N	44	43	84	39
Mean change from baseline to Week 52, (standard deviation)	-0.01 (0.2)	0.01 (0.2)	0.08 (0.2)	0.05 (0.2)

Source: Analysis by Statistical Reviewer Dr. Koh

At Week 52, greater improvement in SF-36 PCS scores, Patient Global VAS scores, and FACIT-Fatigue scores were observed in both TCZ treatment groups as compared to the placebo groups. These analyses were not controlled for multiplicity, and

therefore, the statistical significance of these changes are not discussed. Importantly, the clinical meaningfulness of these changes in the context of GCA have not been established.

6.1.6 Other Endpoints

Annualized relapse rate at Week 52, an exploratory efficacy endpoint, was calculated as the number of flares between the first Clinical GCA assessment and the last Clinical GCA assessment prior to entry into Part 2, divided by the time period in days between the two assessments multiplied by 365.25. For patients who withdrew prior to the Week 52 Clinical GCA assessment, the last available Clinical GCA assessment was used. The mean annualized relapse rate at Week 52 was higher in the PBO+26 wk (1.74/year) and PBO+52 wk (1.30/year), as compared to the TCZ QW (0.41/year) and TCZ Q2W (0.67/year).

The annualized relapse rate as defined by the number of flares where flare is based on investigator determination of signs and symptoms and ESR ≥30 mm/hr attributable to GCA, was lower in the TCZ treatment groups, as compared to the placebo groups. Further, the annualized relapse rate was numerically lower in the TCZ QW group than in the TCZ Q2W group. (b) (4) this exploratory endpoint was not included in the statistical hierarchy, raising the possibility that these observations could be due to chance. Additional considerations are that this analysis does not preserve the integrity of randomization, i.e. uses a post-randomization variable (whether a patients acheves remission) (b) (4)

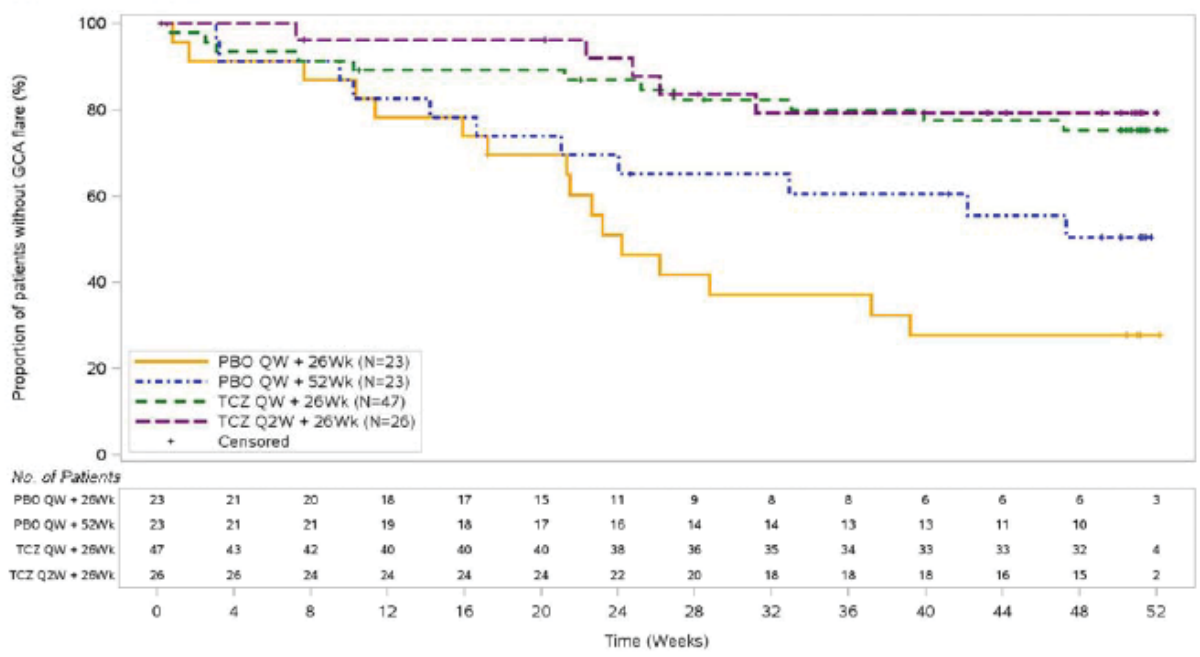
6.1.7 Subpopulations

New Onset Disease vs. Relapsing GCA
Patients with both new-onset GCA and relapsing GCA, defined as GCA diagnosed >6 weeks before the baseline visit and previous treatment with ≥40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at any time, were enrolled in Study WA28119. In patients with new-onset GCA, the proportion of patients in sustained remission at Week 52 was greater than that seen in the overall population, particularly in the placebo groups (PBO+26 wk 21.7%, PBO+52 wk 21.7%, TCZ QW 59.6%, TCZ Q2W 57.7%). In the patients with relapsed GCA, the proportion of patients who achieved sustained remission at Week 52 was lower than that of the overall population, as well as the new-onset patients (PBO+26 wk 7.4%, PBO+52 wk 14.3%, TCZ QW 52.8%, TCZ Q2W 47.8%). In all treatment groups, the proportion of patients in sustained remission at Week 52 was higher in the new-onset patients as compared to those with relapsed disease, and higher in the TCZ treatment groups as compared to the placebo groups.

In the new-onset GCA patients, the median time to first GCA flare after remission was 169 days in the PBO+26 wk group, but was not calculable in the other treatment groups because fewer than 50% of the patients experienced a flare after remission by Week 52. In the relapsing patients, the median time to GCA disease flare following remission was 165 days in the PBO+26 wk group, 274 days in the PBO+52 wk group, and not calculable in the TCZ groups as fewer than 50% of the patients in these treatment groups experienced a flare by Week 52. The time to first GCA flare is presented in the Kaplan-Meier plots in Figure 7. In the new-onset GCA patients, the curves of the placebo and TCZ treatment groups separate with the shortest median time to first flare after remission in the PBO+26 wk group. The TCZ QW and TCZ Q2W curves are similar. In the relapsing GCA patients, the shortest median time to first flare after remission is also in the PBO+26 wk group. In these patients, there is separation of the TCZ QW group from the other treatment groups at approximately Week 12 and continuing through Week 52. There is overlap between the TCZ Q2W group and the PBO+52 wk group until approximately Week 38, after which time, the curves separate, however conclusions are limited based on the small numbers of patients at these later timepoints. This observation can also be confounded by the overall higher median cumulative prednisone doses in patients with new-onset disease than in the patients with relapsing disease in the TCZ treatment groups (see Table 14).

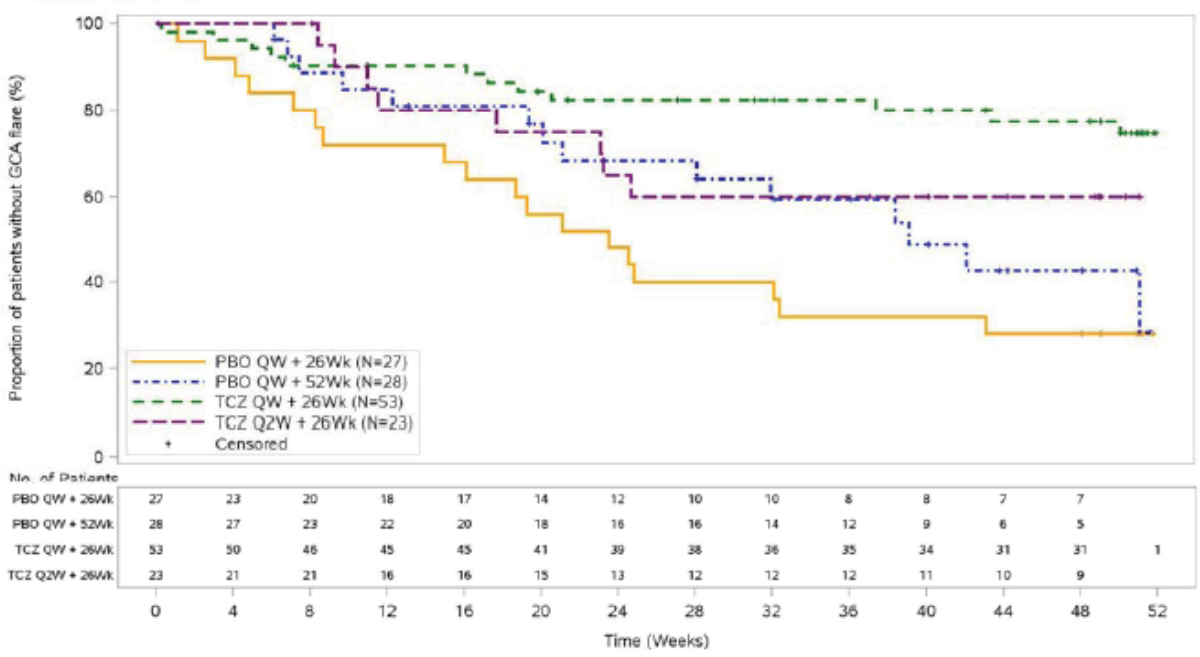
Figure 7: Kaplan-Meier Plot of Time to First GCA Disease Flare after Remission by Disease Status at Baseline (ITT Population)

New-onset Patients



Patients who were never in remission are censored at Day 1.
Patients who withdrew from the study prior to Week 52 are censored from the time of withdrawal.
Program: /opt/BIOSTAT/prod/cn11935e/i28119a/g_fl_km.sas Output: /opt/BIOSTAT/prod/cn11935e/i28119a/reports/g_fl_km_IT_NEWON.pdf 11JUL2016 23:34

Relapsing Patients



Source: Clinical Study Report Figure 6

Similar proportions of patients achieved sustained remission in the TCZ QW as compared to the TCZ Q2W groups in both the new-onset GCA population and the relapsed GCA population. In the analysis of time to first flare after remission, the relapsing patients treated with TCZ QW had a longer time to first flare as compared to the other treatment groups, while in the new-onset patients, the time to first flare was similar between the TCZ QW and TCZ Q2W groups. As stated above, this is no longer a randomized population, limiting conclusions that may be drawn for treatment of patients who are not in remission (b) (4)

Median cumulative prednisone dose was higher in the placebo treated patients in both those with new-onset and relapsing GCA, as compared to the TCZ treatment groups. The patients in the PBO+26 wk group with relapsing disease had higher median cumulative prednisone dose than those with new-onset disease, while the patients with new-onset disease randomized to PBO+52 wk had a slightly higher median cumulative prednisone dose than those with relapsing disease. Patients with new-onset disease in the TCZ treatment groups had higher median cumulative prednisone doses than the patients with relapsing disease. This difference could have potentially contributed to the apparent TCZ dose separation for first GCA disease flare rates observed in TCZ-treated patients with relapsing disease (see Figure 7).

Table 14: Cumulative Prednisone Dose by Disease Status at Baseline (ITT Population)

	PBO+26wk N = 50	PBO+52wk N = 51	TCZ QW N = 100	TCZ Q2W N = 49
New-onset				
Median cumulative prednisone dose, mg	3068.0	3817.5	1942.0	2202.0
Relapsing				
Median cumulative prednisone dose, mg	3860.5	3785.5	1385.0	1568.0

Source: Adapted from Clinical Study Report Table 30

Diagnostic Criteria of GCA

Subgroup analysis was performed based on diagnostic criteria upon which GCA diagnosis was based. Analysis of the subgroup of patients with a GCA diagnosis based on the 1990 ACR classification criteria was consistent with that of the overall population (Table 15). In patients who did not meet the ACR criteria, a greater proportion of patients achieved sustained remission at Week 52 while adhering to the protocol-defined prednisone taper in the TCZ treatment groups (TCZ QW 47.6% and TCZ Q2W 40.0%) as compared to the placebo treatment groups (PBO+26 wk 25.0%, PBO+52 wk 18.1%).

While the response rate in the placebo groups in patients who did not meet ACR classification criteria was higher than that observed in the overall population,

conclusions are limited by the small numbers of patients in the placebo group who did not meet these criteria. There were 12 patients in the PBO+26 wk and 11 patients in the PBO+52 wk groups who did not meet ACR criteria, and of these 3 and 2 patients achieved sustained remission at Week 52, respectively.

The proportion of patients in sustained remission in the subgroup of patients with a positive temporal artery biopsy was similar to that of the overall population (Table 15). Ninety four patients were diagnosed with GCA based on imaging characteristics without a positive temporal artery biopsy. Of these patients, the proportion of patients achieving sustained remission at Week 52 was generally similar to that seen in the overall population, with a higher proportion of patients in the PBO+26 wk and TCZ QW groups meeting this endpoint as compared to that observed in the overall study population. When analyzing patients diagnosed with GCA based on imaging alone without cranial symptoms, a greater proportion of patients in the TCZ QW group (50.0%) as compared to the other treatment groups (PBO+26 wk 25%, PBO+52 wk 28.6%, TCZ Q2W 33.3%) achieved a sustained response at Week 52.

Table 15: Sustained Remission at Week 52 by GCA Diagnostic Criteria (ITT Population)

	PBO+26wk	PBO+52wk	TCZ QW	TCZ Q2W
1990 ACR Classification Criteria, n	38	40	79	39
Sustained remission, n (%)	4 (10.5)	7 (17.5)	46 (58.2)	22 (56.4)
Temporal artery biopsy positive, n	36	29	57	33
Sustained remission, n (%)	4 (11.1)	5 (17.2)	29 (50.9)	18 (54.5)
Positive imaging, n	19	23	50	23
Sustained remission, n (%)	4 (21.1)	4 (17.4)	30 (60.0)	13 (56.5)
Positive imaging only (negative temporal artery biopsy), n	14	21	43	16
Sustained remission, n (%)	3 (21.4)	4 (19.0)	27 (62.8)	8 (50.0)

Source: Reviewer JMP analysis of ABASE dataset using terms ITTFL, HACR, HLVVP, LVVOFL, HTABP, TRT01A, SREMTRFL

In analyses using different diagnostic criteria, including 1990 ACR classification criteria, positive imaging, and temporal artery biopsy, the treatment benefit of the TCZ treatment groups over the placebo treatments is maintained and of similar magnitude with each comparison. The proportion of responders in the TCZ QW and TCZ Q2W groups are generally similar regardless of which diagnostic criteria are applied.

Body Weight

The approved SC TCZ dosing regimen in RA is body weight tiered based on exposore-response information by body weight. To explore a possible association in GCA, the Applicant and the FDA review team explored the efficacy by body weight. Patients with lower body weight were observed to have higher TCZ exposures in the GCA and RA populations. Analysis of patients with GCA who achieved a sustained remission by

Week 52 by body weight showed a trend toward greater response with the TCZ QW regimen in those patients of body weight < 60 kg (TCZ Q2W 38.5%, TCZ QW 59.3%), while a numerically greater proportion of patients in the 60-100 kg weight group responded to TCZ Q2W as compared to TCZ QW (TCZ Q2W 62.5%, TCZ QW 55.7%). There were too few patients in the >100 kg weight group to draw conclusions. Based on this information, weight doesn't appear to consistently impact the response to either TCZ dosing regimen and weight based/tiered dosing is not justified in the overall GCA population. Should both dosing regimens be approved, the selection of TCZ dosing for individual patient should be at the health care provider's discretion based on other clinical considerations (see the next section, Analysis of Clinical Information Relevant to Dosing Recommendations).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Efficacy results in the TCZ QW and TCZ Q2W treatment groups were generally similar. There was a small, but numerically greater proportion of patients in the TCZ QW group, as compared to the TCZ Q2W group, who achieved a sustained remission at Week 52 and adhered to the protocol-defined prednisone taper (56.0% and 53.1%, respectively). In sensitivity analyses, only TCZ QW remained statistically superior to PBO+52 wk when analysis excluded assessment of inflammatory markers. A numerically greater proportion of patients in the TCZ Q2W group experienced flares and received escape prednisone therapy. In evaluating the secondary endpoint of time to first GCA flare after remission, a trend towards better efficacy of the TCZ QW regimen was observed. Time to event analysis of the hazard ratios for the TCZ Q2W versus the TCZ QW was 1.24 (99% CI: 0.63 to 2.44) indicating a trend towards a higher risk of flare in the Q2W group, however, conclusions regarding time to first GCA flare are limited by the non-randomized population of only patients who achieved remission by Week 12. Differences between the arms (or lack thereof) may be due to treatment effects or could be due to differences in the patient characteristics of the subsets who achieved remission on the different arms. In a pre-specified subgroup analysis by disease onset, the difference in proportions of responders between the TCZ QW and TCZ Q2W was numerically greater in the patients with relapsed disease (unadjusted difference in percentage of responders of 5% in relapsing GCA vs. 1.9% in new-onset GCA). In the analysis of time to first flare after remission, the relapsing patients treated with TCZ QW had a longer time to first flare as compared to the other treatment groups, however this analysis has similar limitations as described for the time to first flare after remission for the overall population.

Both the TCZ QW and TCZ Q2W dosing regimens demonstrated consistent improvement on the primary, key secondary, and secondary endpoints over the placebo treatment groups. The observed differences between the two TCZ dosing regimens are small, however there is a trend towards improved response with the TCZ QW dose regimen in sustained remission at Week 52, time to first flare after remission, and cumulative prednisone use. In addition, there is a trend to improvement in patients with relapsing disease who receive TCZ QW. Given the need for aggressive treatment of

GCA to prevent acute and long-term sequelae, and the similar safety profiles of the two regimens, I agree with the proposed dose of TCZ 162 mg SC QW. Of note, safety and immunogenicity were similar between the two TCZ dosing regimens and consistent with the established safety profile for TCZ. A greater proportion of patients experienced serious infections in the TCZ QW compared to TCZ Q2W treatment group. Given these considerations and because there are no significant differences in efficacy between the two TCZ doses, I believe there may be patients for whom the safety profile of TCZ Q2W is more appropriate, based on individual clinical considerations by patient and health care provider. Thus, I also recommend approval of TCZ 162 mg SC Q2W along with the TCZ QW dosing for GCA.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary and secondary endpoints of Study WA28119 were the proportion of patients in sustained remission at Week 52. The results of these analyses are discussed above. The objectives of ongoing Part 2 of the study are exploratory in nature and include assessment of maintenance of remission and annualized relapse rates. While treatment in Part 2 is open label, these data may provide additional information regarding persistence of efficacy upon completion of the study, but are not necessary for the risk benefit assessment for this supplement.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data submitted include the safety results from Study WA28119 for 250 patients treated with double-blind treatment for 52 weeks in Part 1, and 88 patients treated in the ongoing long term extension with at least 100 weeks of total follow-up.

7.1.2 Categorization of Adverse Events

AE was defined, according to ICH guideline for Good Clinical Practice, as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product regardless of causal attribution. SAE was defined as any AE that meets the following criteria: fatal, life threatening (places patient at immediate risk of death), required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, congenital anomaly/birth defect, or was significant medical event in the investigator's judgment.

Adverse events were graded by intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 and by relationship to study treatment. Events related to GCA were not reported as AEs but were captured in the eCRF; however, serious events related to GCA were reported as SAEs. Verbatim terms reported on the eCRF were coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

Adverse events of special interest (AESI) were defined by Standard MedDRA Queries or Adverse Event Grouped Terms (AEGT) as defined by Roche Drug Safety, and include:

- Infections (Infections and Infestations SOC)
- Opportunistic Infections (OI; Roche Standard AEGT Basket)
- Malignancies (Malignant or Unspecified tumors SMQ Narrow)
- Malignancies without NMSC
- Hepatic events (Hepatic Failure, Fibrosis, and Cirrhosis and Other Liver Damage-Related Conditions SMQ Wide or Hepatitis, non-infectious SMQ Wide)
- Stroke (Ischemic Cerebrovascular Conditions SMQ Narrow or Hemorrhagic Cerebrovascular SMQ Narrow)
- Myocardial infarction (MI; MI SMQ Narrow)
- Anaphylactic reaction events (Roche Standard AEGT Basket) occurring immediately after or within 24 hours of TCZ injection
- Anaphylactic reaction events (defined by Anaphylactic Reaction SMQ Narrow) occurring immediately after or within 24 hours of TCZ injection
- Hypersensitivity adverse events (adverse events occurring immediately after or within 24 hours of end of injection that were not deemed “unrelated” to study treatment)
- Gastrointestinal perforations (Gastrointestinal perforation SMQ Wide)
- Gastrointestinal perforations (Gastrointestinal perforation SMQ Wide) confirmed by medical review
- Bleeding events (Hemorrhage terms [excluding laboratory terms] SMQ Wide)
- Demyelinating events (Demyelination SMQ Narrow)

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. A single study has been completed with SC TCZ in GCA. The Applicant has submitted summary data from ML25676, an investigator initiated, single-center study of IV TCZ in patients with newly diagnosed or relapsing GCA (discussed in section 7.7 below).

7.2 Adequacy of Safety Assessments

Safety assessments included AEs, physical examination, vital signs, laboratory studies and immunogenicity as detailed in the Schedule of Assessments in Appendix 2.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of 11April2016 (clinical data cut-off date), Study WA28119 included 250 patients who received study drug across all treatment groups. The median study duration was 358 days in each treatment group (Table 16). The patient-years of exposure were similar in the TCZ Q2W and placebo groups, and nearly twice as high in the TCZ QW group, as expected, given that twice as many patients were randomized to the TCZ QW group.

Compliance with blinded SC study treatment was high with a median dose intensity of 100% in all treatment groups. Sixty-four percent of patients overall did not miss any doses of blinded SC treatment. Median total cumulative dose was approximately twice as high in the TCZ QW (8343 mg) treatment group as the TCZ Q2W group (4212 mg), consistent with the difference in dosing frequency.

Table 16: Exposure to Blinded SC Study Treatment (Safety Population)

	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Patient Years Exposure to DB SC Treatment	44.33	46.03	86.41	43.70
Treatment Duration[1] (D)				
Mean (SD)	324.0 (79.4)	331.6 (83.4)	317.2 (96.7)	324.3 (82.0)
Median	358.0	358.0	358.0	358.0
Dose Intensity[2] (%)				
Mean (SD)	98.5 (3.4)	98.0 (3.3)	97.9 (4.0)	98.7 (2.7)
Median	100.0	100.0	100.0	100.0
Number of doses (n)				
Mean (SD)	46.3 (11.1)	47.1 (11.7)	45.1 (13.7)	46.5 (11.6)
Median	52.0	51.0	51.5	52.0
Total cumulative dose (mg)				
Mean (SD)	0	0	7304.6 (2215.4)	3785.5 (941.0)
Median	0	0	8343	4212
Missed Doses (n)				
None	37 (74.0)	29 (56.9)	58 (58.0)	36 (73.5)
One missed dose	6 (12.0)	12 (23.5)	24 (24.0)	5 (10.2)
Two missed doses	1 (2.0)	0	6 (6.0)	4 (8.2)
Three missed doses	1 (2.0)	4 (7.8)	3 (3.0)	2 (4.1)
Four missed doses	3 (6.0)	4 (7.8)	4 (4.0)	1 (2.0)
At least five missed doses	2 (4.0)	2 (3.9)	5 (5.0)	1 (2.0)

[1]Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
[2]Dose intensity is the number of doses actually received divided by the expected number of doses multiplied by 100
Source: Adapted from Clinical Study Report Table 35

Similarly, compliance to blinded prednisone taper was high; 60% of patients did not miss any capsules of blinded prednisone treatment during the 52-week study period. Median total cumulative dose of prednisone taper medication was similar in all treatment groups receiving the 26 week taper (1323 mg in PBO+26 wk, 1351.5 mg in

TCZ QW, and 1345 mg in TCZ Q2W groups), while the median total cumulative dose was higher in the PBO+52 wk group (2205 mg), consistent with the longer assigned taper regimen. Median total cumulative dose of prednisone (including open-label, blinded prednisone/placebo, escape prednisone, and commercial prednisone for concomitant conditions) was the same in each of the TCZ treatment groups (1862 mg), and higher in the PBO+52 wk (3817.5 mg) and PBO+26 wk (3296.0 mg) treatment groups.

7.2.2 Explorations for Dose Response

Study WA28119 included TCZ QW and Q2W treatment groups, consistent with the two approved dosing regimens for patients with RA.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this submission.

7.2.4 Routine Clinical Testing

Laboratory assessments included:

- Hematology – hemoglobin, hematocrit, red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cells, absolute differential count, and platelet counts
- Chemistry - urea, uric acid, creatinine, glucose, potassium, sodium, chloride, calcium, phosphorous, total protein, albumin, creatine phosphokinase, C3, and C4
- Serum Lipids - total fasting cholesterol and LDL
- Fasting HbA1c
- Liver Profile - AST/SGOT, ALT/SGPT, alkaline phosphatase, and total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN)
- Serology - rheumatoid factor, protein electrophoresis, hepatitis B surface antigen, and hepatitis C virus antibody (at screening only unless clinically indicated during the study)
- Acute-phase Reactants - high-sensitivity CRP (to be assessed at the central laboratory) and ESR (Westergren method; to be assessed at a local laboratory)
- Urinalysis - Dipstick for blood, protein, and glucose (microscopic examination at central laboratory if abnormal and/or applicable)

Twelve-lead ECGs were performed according to the schedule of assessments (Appendix 2). Chest X-rays were obtained at screening, or within the 90 days prior to screening if the chest X-ray was without clinically significant abnormality and in the absence of signs or symptoms of pulmonary disease.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance and interaction workup studies were conducted for this application. For further details, please refer to Section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety profile of tocilizumab in Giant Cell Arteritis was assessed in the context of the known adverse event profile of TCZ in rheumatoid arthritis, and the known safety profiles of other biologic therapies.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during Part 1 of the study. There was one fatal event of aortic dissection reported in Part 2 as of the cutoff date of 11April 2016. The aortic dissection occurred in a 62 year old female with a history of hypertension and relapsing GCA, previously treated with methotrexate and cyclophosphamide, who was randomized to the PBO+26 week group. She experienced GCA flares on Study Days 120 and 238 and received escape prednisone. She entered Part 2 of the study and initiated open-label tocilizumab. On Study Day 542, she experienced a cerebrovascular accident, and was subsequently discharged from the hospital. On Study Day 573, she died; an autopsy revealed an ascending aortic dissection with pericardial tamponade. Aortic dissection is a recognized consequence of large vessel GCA. This event is most likely related to her underlying GCA.

7.3.2 Nonfatal Serious Adverse Events

Seventy three SAEs were reported by 46 patients (18.4%) in Part 1 of Study WA28119. The proportions of patients with ≥ 1 SAEs were higher in the PBO treatment groups as compared to the TCZ QW and TCZ Q2W treatment groups (Table 17). SAEs in the Infections and Infestations SOC and Vascular Disorders SOC were most frequently reported. SAEs in the Infections and Infestations SOC were reported by more patients in the PBO+52 wk and TCZ QW treatment groups (11.8% and 7.0%, respectively) as compared to the TCZ Q2W and PBO+26 wk groups (4.1% and 4.0%, respectively). The most frequently reported preferred terms were gastroenteritis and herpes zoster, each reported in 2 patients in the PBO+52 wk and 1 patient in the TCZ QW treatment groups. There was 1 additional patient who experienced genital herpes zoster in the PBO+52 wk treatment group. Pneumonia was reported by 1 patient each in the PBO+26 wk and TCZ QW groups and pneumonia haemophilus was reported in 1 patient in the PBO+26 wk group. In the Vascular Disorders SOC, temporal arteritis was reported as an SAE by 4 patients, one in each treatment group, while hypertensive crisis was reported by 2 patients in the TCZ QW treatment group. The events of hypertensive crisis occurred in one patient with a history of hypertension treated with 3 antihypertensive agents as well

as a history of Cushing's syndrome and renal failure, and in another patient with a history of hypertension treated with 5 antihypertensive agents; these comorbidities may have played a role in the events.

All other SAEs occurred in single patients.

Table 17: Patients with ≥1 SAEs by SOC and PT, reported by ≥1 patient in any treatment group in Part 1 (Safety Population)

System organ class Preferred term	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Patients with ≥ 1 SAE	**11 (22.0)**	**13 (25.5)**	**15 (15.0)**	**7 (14.3)**
Total # of SAEs	**15**	**21**	**27**	**10**
Infections And Infestations	**2 (4.0)**	**6 (11.8)**	**7 (7.0)**	**2 (4.1)**
Gastroenteritis	0	2 (3.9)	1 (1.0)	0
Herpes Zoster	0	2 (3.9)	1 (1.0)	0
Cellulitis	0	0	1 (1.0)	1 (2.0)
Pneumonia	1 (2.0)	0	1 (1.0)	0
Vascular Disorders	**2 (4.0)**	**1 (2.0)**	**4 (4.0)**	**2 (4.1)**
Temporal Arteritis	1 (2.0)	1 (2.0)	1 (1.0)	1 (2.0)
Hypertensive Crisis	0	0	2 (2.0)	0
Respiratory, Thoracic And Mediastinal Disorders	**2 (4.0)**	**2 (3.9)**	**2 (2.0)**	**1 (2.0)**
Cardiac Disorders	**0**	**2 (3.9)**	**2 (2.0)**	**0**
Injury, Poisoning and Procedural Complications	**1 (2.0)**	**0**	**3 (3.0)**	**1 (2.0)**
Nervous System Disorders	**2 (4.0)**	**1 (2.0)**	**1 (1.0)**	**1 (2.0)**
Gastrointestinal Disorders	**2 (4.0)**	**0**	**1 (1.0)**	**0**
Gastritis Erosive	1 (2.0)	0	0	0
Musculoskeletal And Connective Tissue Disorders	**1 (2.0)**	**2 (3.9)**	**1 (1.0)**	**0**
Eye Disorders	**1 (2.0)**	**1 (2.0)**	**0**	**0**
Cataract	0	1 (2.0)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**1 (2.0)**	**1 (2.0)**	**0**	**1 (2.0)**
Immune System Disorders	**0**	**0**	**1 (1.0)**	**1 (2.0)**
Metabolism And Nutrition Disorders	**0**	**1 (2.0)**	**0**	**1 (2.0)**
Other*				

*Other includes single patients with SAEs of Cholangitis Infective, Chronic Sinusitis, Erysipelas, Genital Herpes Zoster, Pneumonia Haemophilus, Pyelonephritis, Respiratory Tract Infection, Urinary Tract Infection, Urosepsis, Deep vein thrombosis, Dry gangrene, Hypertension, Asthma, Dyspnoea, Dyspnoea exertional, nasal inflammation, Oropharyngeal pain, Pleural effusion, Pulmonary Embolism, Aortic Valve Stenosis, Cardiac failure, Cardiac failure chronic, Supraventricular tachycardia, Tachyarryhthmia, alcohol poisoning, laceration, meniscus injury, postoperative wound complication, tendon rupture, headache, paraesthesia, syncope, thrombotic stroke, transient ischaemic attack, diarrhea, stomatitis, arthralgia, fibromyalgia, osteoarthritis, tendon pain, glaucoma, breast cancer, malignant melanoma, ovarian adenoma, drug hypersensitivity, hypersensitivity, anxiety, stress, hepatic enzyme increased, and renal impairment
Source: Reviewer JMP analysis, AAE dataset, using terms AESER=Y, TRT01A, AESOC, AEDECOD, USUBJ

A greater proportion of patients in the PBO treatment groups reported SAEs as compared to the TCZ groups. The most frequently reported SAEs were in the Infections and Infestations SOC. Treatment with corticosteroids is associated with an increased risk of infections and the patients in the PBO treatment groups received higher doses of steroids than those in the TCZ treatment groups. Treatment with TCZ is also associated with an increased risk of serious infections. Based on Table 17, no numerical imbalances are observed to suggest an increase in the risk of infections with TCZ above that associated with steroid use in patients with GCA. A greater proportion of patients had infectious SAEs in the TCZ QW treatment group as compared to the TCZ Q2W group, however, these differences are based on small numbers of patients. Two events of hypertensive crisis occurred in the TCZ QW treatment group only, however, these patients both had a history of significant hypertension as evidenced by the number of antihypertensives required for treatment. Overall, review of the SAEs in Study WA28119 is consistent with the known safety profile of TCZ.

Rates of SAE events per 100 patient years (PY) was higher in the GCA population (TCZ QW: 29.1, TCZ Q2W: 21.9 events per 100 PY) than that observed in the IV TCZ LTE all-exposure RA population (14.43 events per 100 PY). Rates of SAEs within the Infections and Infestations SOC were higher in the TCZ QW group in Study WA28119 (9.7 events per 100 PY) and similar in the TCZ Q2W group in Study WA28119 (4.4 events per 100 PY) and the IV TCZ RA population (4.4 events per 100 PY). The increase in rates of SAE may be related to multiple factors including the older age and higher doses of concomitant steroids in the GCA patients, as well as other disease related characteristics, as compared to RA patients. In addition, comparisons between these populations are limited by the relatively short duration of follow-up in Study WA28119.

In Part 2, 18 of 88 patients (20.5%) reported 23 SAEs. The events reported by the greatest proportion of patients occurred in the Vascular Disorders SOC, including events of hematoma (2 patients), temporal arteritis (2), aortic dissection (1, discussed under 7.3.1 Deaths above), and peripheral artery occlusion (1). SAEs of temporal arteritis occurred in 1 patient each in the TCZ QW and TCZ Q2W groups; neither was receiving OL TCZ at the time of the event. Cerebrovascular accident and peripheral artery occlusion occurred in 1 patient each in the PBO+26 wk treatment group, while 1 patient each in the PBO+52 wk and TCZ QW groups reported angina pectoris; all were receiving OL TCZ at the time of the events. The patient in the PBO+52 wk group who experienced angina pectoris, also reported an SAE of troponin increased on the same day. SAEs in Part 2 within the Infections and Infestations SOC include gastroenteritis (1 TCZ QW, not on OL TCZ) and urosepsis (1 PBO+26 wk on OL TCZ). Two patients reported arthritis (1 each in TCZ QW and Q2W). Three events (glaucoma, syncope, and cardiac failure) occurred in patients never exposed to TCZ. Other SAEs in Part 2 up to the time of the data cut off were singular events. Analysis of the data from Part 2 is limited by differential follow-up and exposure to TCZ in the relatively small numbers of patients in each treatment group until the data cut off. Overall, the SAEs observed in

Part 2 until the data cut off are consistent with those observed in Part 1, as well as the known safety profile of TCZ.

7.3.3 Dropouts and/or Discontinuations

Eleven patients (4.4%) discontinued the study due to AEs, including 2 patients in the PBO+26 wk treatment group (breast cancer, muscular weakness), 6 patients in the TCZ QW group (neutropenia, spondylitis, osteoarthritis, pneumonia haemophilus, blood creatine phosphokinase increased, and herpes zoster), and 3 in the TCZ Q2W group (rash, hypersensitivity, optic ischaemic neuropathy). Twelve patients discontinued Part 1 of the study due to AEs, including the 11 patients described and one additional patient in the TCZ QW group who discontinued Part 1 due to AE, but later discontinued the study due to physician decision.

The Applicant has provided multiple variables for different types of discontinuations (discontinuations from Part 1, discontinuation from study, discontinuation from blinded treatment, discontinuation from blinded TCZ/placebo). Analysis using these variables is not always consistent. For instance, 15 patients discontinued blinded treatment (including blinded TCZ/placebo, blinded prednisone, or open-label/escape prednisone treatment) using the DISCDBR variable and term “adverse event”, however, 19 patients discontinued blinded TCZ/placebo using AEACN1 variable and “drug withdrawn”. Therefore, a greater number of patients discontinued blinded TCZ/placebo than blinded TCZ/placebo, blinded prednisone, or open-label/escape prednisone treatment. This is likely a coding error. The Applicant explains “that the information is derived from two separate eCRF pages and not necessarily consistent between pages.” In addition, when using the variable AEWITH, 23 patients are identified who experienced an AE leading to withdrawal of study treatment. A summary of AEs leading to discontinuation of blinded study treatment using the variable that identifies the broadest number of patients (AEWITH) is presented in Appendix 3. AEs leading to discontinuation of blinded TCZ treatment are discussed further below.

AEs led to withdrawal of blinded TCZ/placebo, blinded prednisone, or open-label/escape prednisone treatment in 23 patients (PBO+26 wk: 6 patients, PBO+52 wk: 0, TCZ QW: 11, and TCZ Q2W: 6). The AEs that led to withdrawal of blinded TCZ/placebo, blinded prednisone, or open-label/escape prednisone are presented by SOC and PT in Appendix 3. There were 4 patients who discontinued Part 1 for reasons of AE, but did not discontinue double blind treatment for adverse events; these patients had reasons for discontinuation from double-blind treatment attributed to ‘other’ (10490), ‘physician decision’ (10051), ‘withdrawal by subject’ (10181), and ‘lack of efficacy’ (10281).

AEs leading to withdrawal from blinded TCZ/placebo treatment were reported in 19 patients (7.6%) and are presented in Table 18. A greater proportion of patients in the TCZ QW and TCZ Q2W groups reported AEs leading to withdrawal from blinded TCZ/placebo treatment (11.0% and 10.2%, respectively), as compared to the PBO+26

wk treatment group (6.0%) and PBO+52 wk group (0%). The greatest proportion of patients discontinued treatment due to AEs within the Infections and Infestations SOC. The only AE occurring in more than 1 patient was pneumonia, reported in 2 patients in the TCZ QW group, with reported terms pneumonia and Haemophilus pneumonia. Other adverse events leading to discontinuation were singular in nature. Infectious AEs and AEs within the Blood and Lymphatic Disorders SOC were most frequently reported by patients in the TCZ QW treatment group as compared to the other treatment groups, however the numbers of patients reporting events are small.

Table 18: AEs Leading to Blinded TCZ/Placebo Discontinuation in Part 1 (Safety Population)

System organ class Preferred term	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Number of patients with AEs leading to blinded TCZ/placebo discontinuation	**3 (6.0)**	**0**	**11 (11.0)**	**5 (10.2)**
Infections and Infestations	**0**	**0**	**5 (5.0)**	**1 (2.0)**
Gastroenteritis	0	0	1[2] (1.0)	0
Cellulitis	0	0	0	1[2] (2.0)
Chronic Sinusitis	0	0	1[2] (1.0)	0
Herpes Zoster	0	0	1 (1.0)	0
Pneumonia	0	0	1[2] (1.0)	0
Pneumonia Haemophilus	0	0	1[1,2] (1.0)	0
Sepsis	0	0	1 (1.0)	0
Musculoskeletal And Connective Tissue Disorders	**1 (2.0)**	**0**	**3 (3.0)**	**0**
Muscular Weakness	1[1] (2.0)	0	0	0
Osteoarthritis	0	0	1[1] (1.0)	0
Pain in Extremity	0	0	1 (1.0)	0
Spondylitis	0	0	1[1] (1.0)	0
Vascular Disorders	**0**	**0**	**1 (1.0)**	**2 (4.1)**
Deep Vein Thrombosis	0	0	1 (1.0)	0
Dry Gangrene	0	0	0	1[2] (2.0)
Temporal Arteritis	0	0	0	1[1,2] (2.0)
Blood and lymphatic disorders	**0**	**0**	**2 (2.0)**	**0**
Anaemia	0	0	1 (1.0)	0
Leukocytosis	0	0	1 (1.0)	0
Neutropenia	0	0	1[1] (1.0)	0
Gastrointestinal disorders	**1 (2.0)**	**0**	**1 (1.0)**	**0**
Nausea	0	0	1 (1.0)	0
Stomatitis	1[2] (2.0)	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**1 (2.0)**	**0**	**1 (1.0)**	**0**
Breast cancer	1[1,2] (2.0)	0	0	0
Marginal Zone Lymphoma	0	0	1 (1.0)	0
Respiratory, Thoracic And Mediastinal Disorders	**1 (2.0)**	**0**	**1 (1.0)**	**0**
Nasal inflammation	1[2] (2.0)	0	0	0
Pleural effusion	0	0	1[2] (1.0)	0
Eye Disorders	**0**	**0**	**0**	**1 (2.0)**
Optic Ischaemic Neuropathy	0	0	0	1[1] (2.0)
General Disorders and Administration Site Conditions	**0**	**0**	**1 (1.0)**	**0**
Oedema Peripheral	0	0	1	0
Immune system disorders	**0**	**0**	**0**	**1 (2.0)**

Hypersensitivity	0	0	0	1[1,2] (2.0)
Injury, Poisoning and Procedural Complications	**0**	**0**	**1 (1.0)**	**0**
Tendon Rupture	0	0	1[2] (1.0)	0
Investigations	**0**	**0**	**1 (1.0)**	**0**
Blood Creatine Phosphokinase Increased	0	0	1[1] (1.0)	0
Psychiatric disorders	**0**	**0**	**1 (1.0)**	**0**
Anxiety	0	0	1 (1.0)	0
Skin and subc. Tissues	**0**	**0**	**0**	**1 (2.0)**
Rash	0	0	0	1[1] (2.0)

[1] Led to study discontinuation
[2] SAE
Source: Reviewer JMP analysis, AAE dataset using terms AEACN1= 'Drug Withdrawn' , USUBJID, AESOC, AEDECOD, TRT01A
Applicant Response to IR dated23 Jan 2017

In Part 2, 1 patient died due to an SAE of aortic dissection. One patient who received TCZ Q2W in Part 1 discontinued open-label/escape prednisone due to an AE of hypertension, however none of the patients discontinued open-label TCZ treatment.

The proportion of patients with AEs leading to Part 1 and study discontinuation was similar across the TCZ treatment groups and the PBO+26 wk group. No patients discontinued treatment or Part 1 due to an AE in the PBO+52 wk group. A greater proportion of patients discontinued blinded TCZ/placebo treatment in the TCZ QW treatment arm, however observed differences are due to small numbers of patients and single events. Other than pneumonia that occurred in 2 patients in the TCZ QW group, events occurred in single patients. The rates of AEs leading TCZ withdrawal were higher in Study WA28119 (23.7 events per 100 PY and 13.2 events per 100 PY for TCZ QW and TCZ Q2W, respectively) as compared to the RA LTE population (4.9 events per 100 PY). The most common AE leading to TCZ withdrawal in the RA LTE population were also in the Infections and Infestations SOC (pneumonia and cellulitis) and Investigations (elevated transaminases). Differences in AE rates leading to TCZ withdrawal may be related to differences in underlying disease, concomitant steroid doses, other concomitant medications, patient demographics, and/or other differences.

Seventy two patients (28.8%) experienced 123 AEs leading to dose interruption or modification of blinded TCZ, blinded prednisone or open-label/escape prednisone during the study, including 12 (24.0%) patients in the PBO+26 wk group, 17 (33.3%) in the PBO+52 wk group, 33 (33.0%) patients who received TCZ QW, and 10 (20.4%) patients in the TCZ Q2W treatment group. Fifty seven patients (22.8%) experienced 99 AEs leading to dose interruption or modification of blinded TCZ, including 10 (20.0%) patients in PBO+26 wk, 11 (22.0%) patients in the PBO+52 wk, 28 (28.0%) patients in the TCZ QW, and 8 (16.0%) patients in the TCZ Q2W treatment groups. AEs leading to dose interruption or modification that were reported in more than 1 patient in any treatment group are listed in Table 19. All other AEs leading to dose interruption/modification occurred in single patients.

Table 19: Patients with AEs leading to TCZ/placebo dose modification or interruption in ≥ 1 patient in Part 1 (Safety Population)

Preferred term	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Number of patients with TEAEs leading to study treatment interruption/modification	**10 (20.0)**	**11 (22.0)**	**28 (28.0)**	**8 (16.0)**
Nasopharyngitis	0	1 (2.0)	4 (4.0)	1 (2.0)
Urinary Tract Infection	1 (2.0)	1 (2.0)	2 (2.0)	0
Alanine Aminotransferase Increased	0	0	4 (4.0)	1 (2.0)
Cystitis	1 (2.0)	1 (2.0)	0	0
Upper Respiratory Tract Infection	1 (2.0)	0	3 (3.0)	1 (2.0)
Bronchitis	0	2 (3.9)	1 (1.0)	1 (2.0)
Aspartate Aminotransferase Increased	0	0	3 (3.0)	0
Erysipelas	1 (2.0)	0	1 (1.0)	1 (2.0)
Laryngitis	0	1 (2.0)	1 (1.0)	0
Neutropenia	0	0	3 (3.0)	0
Herpes Zoster/Herpes Virus Infection	1 (2.0)	1 (2.0)	1 (1.0)	0
Leukopenia	0	0	2 (2.0)	0
Lower Respiratory Tract Infection	0	0	2 (2.0)	0
Pyrexia	1 (2.0)	1 (2.0)	0	0
Sinusitis	0	1 (2.0)	0	1 (2.0)

Source: Reviewer JMP analysis AAE dataset, using terms AEACN1, AEDECOD, USUBJID, TRT01A

The proportion of patients with AEs leading to dose interruption or modification of blinded TCZ/placebo was similar across treatment groups, with a somewhat greater number of patients in the TCZ QW group and fewer patients in the TCZ Q2W as compared to the placebo groups. A greater proportion of patients in the TCZ QW group reported nasopharyngitis, ALT increased, AST increased, and neutropenia, leading to dose interruption/modification as compared to the other treatment groups. These are consistent with the known safety profile of tocilizumab.

7.3.4 Significant Adverse Events

AESI were defined based on safety concerns for the GCA population, findings from clinical studies of TCZ in RA, and the safety profile of other biologic agents used to treat RA. AESI included but were not limited to, infections, opportunistic infections, malignancies, hepatic events, hypersensitivity, ISRs, stroke, myocardial infarction, anaphylactic reactions, GI perforations, bleeding events, and demyelinating events.

The proportions of patients with adverse events of special interest are summarized in Table 20. There were no reports of serious hepatic events, serious myocardial infarction events, serious gastrointestinal perforation events, serious bleeding events, or serious demyelinating AEs during the double-blind portion of the study.

Table 20: Adverse Events of Special Interest in Part 1 (Safety Population)

Number of patients with:	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Infections	38 (76.0)	33 (64.7)	75 (75.0)	36 (73.5)
Serious infections	2 (4.0)	6 (11.8)	7 (7.0)	2 (4.1)
Opportunistic infections	0	2 (3.9)	0	1 (2.0)
Malignancy	1 (2.0)	1 (2.0)	1 (1.0)	0
Serious Stroke	0	1 (2.0)	0	1 (2.0)
Hypersensitivity/Drug hypersensitivity	1 (2.0)	1 (2.0)	1 (1.0)	2 (4.1)
Anaphylaxis (SMQN)	0	0	0	0
Anaphylaxis (Sampson)	0	0	0	1 (2.0)
Injection site reactions	5 (10.0)	1 (2.0)	6 (6.0)	7 (14.3)

Source: Adapted from Clinical Study Report Table 34

Infections

There were 434 AEs reported in the Infections and Infestations SOC that occurred in 182 patients, balanced across the treatment groups (Table 20). The proportion of patients reporting events by preferred term were also generally balanced across the treatment groups. The most frequently reported infections based on number of patients reporting events included nasopharyngitis (PBO+26 wk: 9 (18.0%); PBO+52 wk: 13 (25.5%); TCZ QW: 29 (29.0%); TCZ Q2W: 12 (24.5%)), upper respiratory tract infection (PBO+26 wk: 5 (10.0%); PBO+52 wk: 7 (13.7%); TCZ QW: 10 (10.0%); TCZ Q2W: 6 (12.2%)), bronchitis (PBO+26 wk: 5 (10.0%); PBO+52 wk: 5 (9.8%); TCZ QW: 8 (8.0%); TCZ Q2W: 4 (8.2%)), and urinary tract infections (PBO+26 wk: 2 (4.0%); PBO+52 wk: 4 (7.8%); TCZ QW: 10 (10.0%); TCZ Q2W: 4 (8.2%)). Cystitis was reported by 7 patients (7.0%) in the TCZ QW group, 2 patients (4.0%) in the PBO+26 wk group, 3 patients (5.9%) in PBO+52 wk group, and no patients in the TCZ Q2W group. Fungal skin infection was reported in 4 patients (4.0%) in the TCZ QW group and did not occur in the other treatment groups.

Seventeen subjects experienced 19 serious infectious AEs. The proportion of patients reporting serious infectious AEs was similar across the treatment groups (Table 20). Events occurring in more than one patient include cellulitis (1 TCZ QW, 1 TCZ Q2W), gastroenteritis (2 PBO+52 wk, 1 TCZ QW), herpes zoster (2 PBO+52 wk, 1 TCZ QW), and pneumonia (1 PBO+26 wk, 1 TCZ QW). Other serious infections included infective cholangitis, chronic sinusitis, erysipelas, genital herpes zoster, pneumonia haemophilus, pyelonephritis, respiratory tract infection, urinary tract infection, and urosepsis in 1 patient each. One patient experienced 3 serious infectious events of pyelonephritis, urinary tract infection, and urosepsis. No other patients experienced more than one serious infection.

Seven patients discontinued treatment with blinded TCZ/placebo, blinded prednisone, or open-label/escape prednisone treatment due to infectious AEs, including 5 patients in the TCZ QW group (pneumonia, chronic sinusitis, gastroenteritis, herpes zoster, and pneumonia hemophilus/sepsis), 1 patient in the TCZ Q2W group (cellulitis), and 1

patient in the PBO+26 wk group (pneumonia). Dose interruption or modification occurred in 42 patients due to infectious AEs, and occurred more frequently in the TCZ QW group (18 patients, 18.0%) and PBO+52 wk (10 patients, 19.6%), as compared to the PBO+26 wk and TCZ Q2W groups (7 patients each, 14.0%).

Opportunistic Infections
There were 4 opportunistic infections reported, including 1 patient (PBO+52 wk) with cytomegalovirus infection, 1 patient (PBO+52 wk) with genital herpes zoster, and 1 patient (TCZ Q2W) with events of laryngitis fungal and oropharyngeal candidiasis. Herpes zoster was reported in 5 patients (5.0%) in the TCZ QW group, 2 patients (4.1%) in the TCZ Q2W, 2 patients (3.9%) in the PBO+52 wk, and 0 patients in the PBO+26 wk. Three patients had serious herpes zoster infections. There were no reports of tuberculosis.

In Part 2, infections were reported in a similar proportion of patients in each Part 1 treatment group (16 patients who received PBO+26 wk in Part 1, 18 PBO+52 wk in Part 1, 30 TCZ QW, and 14 in TCZ Q2W). Serious infections occurred in 2 patients; 1 patient in who received TCZ QW in Part 1, not receiving OL TCZ, reported gastroenteritis and 1 patient in the PBO+26 wk in Part 1 on OL TCZ experienced urosepsis. There were no opportunistic infections reported in Part 2; however, there were 4 patients with herpes zoster (1 PBO+26 wk, 3 TCZ QW), of which only 1 patient in the TCZ QW group was receiving OL TCZ.

The PBO+52 wk treatment group had a lower proportion of patients who reported infections, but a higher proportion of patients who reported serious infections and opportunistic infections. These differences were based on small numbers of patients. The proportion of patients reporting infectious AEs, serious infectious AEs, and opportunistic infections were generally similar across the other treatment groups, with a small numerical increase in serious infections in the TCZ QW group as compared to the TCZ Q2W and PBO+26 wk treatment groups. The types of infections observed in Study WA28119 are consistent with the known safety profile of TCZ. Rates of infections were higher in Study WA28119 (200.2 infections 160.2 infections per 100 PY in the TCZ QW and TCZ Q2W groups, respectively) as compared to the RA LTE population (92.7 infections per 100 PY), while rates of serious infections were higher in the GCA TCZ QW group (9.7 events per 100 PY) and the same in the TCZ Q2W and RA LTE groups (4.4 events per 100 PY). The increased rates of infection relative to the RA population are likely related to the older age and higher concomitant steroid use in the GCA population, among other differences in the populations.

Malignancies
Malignancies were reported in 3 patients during Part 1 of Study WA28119. One male patient (2.0%) in the PBO+26 wk treatment group reported breast cancer and renal neoplasm, while one patient (2.0%) in the PBO+52 wk group reported malignant melanoma and one patient (1.0%) in the TCZ QW group reported marginal zone

lymphoma. The events of breast cancer and malignant melanoma were reported as SAEs.

In Part 2, there were 3 additional malignancies reported including invasive ductal breast carcinoma in 1 patient who received TCZ QW during Part 1, and basal cell skin cancer in 1 patient each in the TCZ QW and PBO+26 wk groups. None of the patients were receiving OL TCZ in Part 2. One additional patient randomized to TCZ QW in Part 1 reported a basal cell skin cancer approximately 5 months after discontinuation of TCZ.

Serious stroke events
One patient in the TCZ Q2W treatment group, who had previously discontinued blinded treatment for cellulitis and dry gangrene, experienced a Grade 4 thrombotic stroke. The patient had multiple risk factors for thrombosis and cardiovascular events. One patient in the PBO+52 wk group, who had a history of supraventricular tachycardia, reported a Grade 3 transient ischemic attack.

In Part 2, 1 patient in the PBO+26 wk treatment group who received OL TCZ in Part 2, experienced a cerebrovascular accident reported as apoplexy.

Myocardial infarction
There were no reports of myocardial infarction in Part 1. One patient in the PBO+26 wk reported angina pectoris, while 2 patients in the PBO+52 wk reported heart failure.

In Part 2, one patient (PBO+52 wk in Part 1, receiving OL TCZ in Part 2) experienced events of angina pectoris, vomiting, and elevated troponin on study day 697. Several days later, the patient experienced events of coronary atherosclerosis and coronary artery disease. The events of angina and elevated troponin were reported to be serious. These events are consistent with a myocardial infarction.

Hepatic events
In Part 1, there were no events of liver failure or liver damage by SMQW analysis. In Part 2, two patients reported events of hepatic steatosis; both received TCZ QW in the double blind portion of the study only.

GI perforations
There were no GI perforations in Parts 1 or 2 through the data cut.

Bleeding events
In Part 1, there were 67 bleeding events in 51 patients (12 PBO+26 wk, 8 PBO+52 wk, 20 TCZ QW, and 11 TCZ Q2W). None of the events were serious. There were 6 Grade 2 events, including contusion in 1 patient on TCZ QW, ecchymosis in 1 patient on PBO+52 wk, and hematoma in 4 patients on TCZ QW, and 2 Grade 3 events, including bone contusion and hemarthrosis in 2 patients receiving TCZ QW.

In Part 2, there were 6 bleeding events in 5 patients. Two patients (TCZ QW and TCZ Q2W, both on OL TCZ) experienced serious hematomas and 1 patient (PBO+52 wk, on OL TCZ) reported a non-serious hematoma. One patient (TCZ QW on OL TCZ) had non-serious events of hemorrhage and contusion and one patient (PBO+26 wk, not on OL TCZ) had a non-serious hemorrhoidal hemorrhage.

Serious Demyelinating
In Part 2, there was a single event of optic neuritis in a patient who received TCZ QW during Part 1 and OL TCZ in Part 2. This is likely a disease-related complication.

Hypersensitivity
Hypersensitivity reactions were those that occurred within 24 hours of an injection, excluding ISRs, and were not deemed "unrelated" to study treatment. Using this approach, potential hypersensitivity reactions occurred in 13 patients receiving TCZ QW, 6 patients receiving TCZ Q2W, 6 patients receiving PBO+26 wk, and 3 patients receiving PBO+52 wk, based on reviewer analysis. The most frequently reported events were headache (5 patients), dizziness (4 patients), rash (3 patients), back pain (2), bronchitis (2), herpes zoster (2), hyperhidrosis (2), and upper respiratory tract infection (2). All other events were singular. The events occurred across the treatment groups, except back pain and hyperhidrosis that were reported by 2 patients each in the TCZ QW group only. Reviewer analysis of events that occurred within 24 hours of an injection, excluding ISRs, without consideration of relatedness, identifies similar types of events generally balanced across the different treatment groups.

A preferred term of hypersensitivity was reported in 1 patient in the TCZ Q2W treatment group, while drug hypersensitivity was reported in 1 patient in each treatment group. One event of drug hypersensitivity (TCZ QW) and 1 event of hypersensitivity (TCZ Q2W) were considered serious. The serious event of hypersensitivity was both an SAE and an AE leading to discontinuation. In addition, 1 patient in the TCZ Q2W group discontinued blinded study treatment due to a Grade 3 rash.

Analysis of adverse events using the narrow SMQ for 'hypersensitivity" did not demonstrate significant differences across the treatment groups. Hypersensitivity reactions were not evaluated during Part 2.

Anaphylaxis
One patient (TCZ Q2W) met Sampson's criteria based on AEs of eye pruritus and dyspnea. The events were not reported as serious and not considered related to study treatment by the investigator. The event of dyspnea resolved after 1 day and the event of eye pruritus resolved after 290 days. Anaphylaxis was also evaluated by the Roche Standard AEGT Basket and SMQ Narrow analysis for events occurring immediately after or within 24 hours of TCZ injection; these analyses did not identify cases of anaphylaxis. No anaphylactic AEs were reported for Part 2.

ISR

Nineteen patients reported AEs of injection site reactions (22 events). The proportion of patients reporting ISR was not more frequent in patients receiving TCZ QW, and the overall proportions of patients reporting AEs of ISR were low (PBO+26 wk: 10.0%, PBO+52 wk: 2.0%, TCZ QW: 6.0%, and TCZ Q2W: 14.3%). Two patients experienced Grade 2 events (1 event of erythema in the TCZ QW group, 1 injection site pain in PBO+26 wk group), while all other ISRs were Grade 1 in severity. No ISR AEs were reported as serious. ISRs reported in more than 1 patient include injection site haemoatoma (1 PBO+52 wk, 1 TCZ QW), injection site pain (1 PBO+26 wk, 1 TCZ Q2W), injection site pruritus (2 TCZ Q2W), and injection site reaction (2 TCZ Q2W). There were no injection site reactions reported as adverse events in Part 2. The proportion of patients reporting ISR was similar to that reported in the RA population (b) (4) (TCZ Q2W 7.1%, TCZ QW 10.1%).

7.3.5 Submission Specific Primary Safety Concerns

Refer to section 7.3.4 for discussion of AESI.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Two thousand one hundred and ninety eight (2198) AEs were reported by 240 patients during Part 1. Patients reporting AEs was generally balanced across the treatment groups (Table 21). AEs were most frequently reported within the Infections and Infestations SOC, Musculoskeletal and Connective Tissue Disorders SOC, and Nervous System Disorders SOC and reported by similar proportions of patients in each treatment group. The most frequently reported PTs within the Infections and Infestations SOC are discussed in Section 7.3.4 above. The most frequently reported PTs within the Musculoskeletal and Connective Tissue Disorders SOC include arthralgia, back pain, musculoskeletal pain, and pain in extremity and the most reported PTs within the Nervous System Disorders SOC are headache, dizziness, and paraesthesia. AEs reported in ≥5% of the safety population are listed by PT in Table 21. AEs occurring more frequently in patients receiving TCZ include hypertension (12.0% and 12.2% in the TCZ QW and Q2W vs. 8.0% and 7.8% in the PBO+26 wk and PBO+52 wk groups) and urinary tract infection (10.0% and 8.2% in the TCZ QW and Q2W vs. 4.0% and 7.8% in the PBO+26 wk and PBO+52 wk groups). Oedema peripheral, dizziness, alopecia, rash, rhinitis, and oral herpes were reported by greater numbers of patients in the TCZ Q2W group compared to the other treatment groups, including TCZ QW, however, the differences observed are due to small numbers of patients.

Table 21: Adverse Events by Preferred Term Occurring in ≥ 5% of the Safety Population (Part 1)

Preferred term	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Patients with ≥ 1 AEs	**48 (96.0)**	**47 (92.2)**	**98 (98.0)**	**47 (95.9)**
Total number of events, n	**470**	**486**	**810**	**432**
Headache	16 (32.0)	12 (23.5)	27 (27.0)	10 (20.4)
Nasopharyngitis	9 (18.0)	13 (25.5)	29 (29.0)	12 (24.5)
Oedema Peripheral	8 (16.0)	6 (11.8)	16 (16.0)	12 (24.5)
Arthralgia	11 (22.0)	8 (15.7)	13 (13.0)	8 (16.3)
Back Pain	7 (14.0)	10 (19.6)	14 (14.0)	7 (14.3)
Dizziness	6 (12.0)	8 (15.7)	6 (6.0)	10 (20.4)
Diarrhoea	8 (16.0)	5 (9.8)	12 (12.0)	3 (6.1)
Upper Respiratory Tract Infection	5 (10.0)	7 (13.7)	10 (10.0)	6 (12.2)
Hypertension	4 (8.0)	4 (7.8)	12 (12.0)	6 (12.2)
Musculoskeletal Pain	5 (10.0)	2 (3.9)	12 (12.0)	6 (12.2)
Fatigue	8 (16.0)	3 (5.9)	8 (8.0)	5 (10.2)
Oropharyngeal Pain	5 (10.0)	8 (15.7)	7 (7.0)	4 (8.2)
Pain In Extremity	5 (10.0)	5 (9.8)	8 (8.0)	5 (10.2)
Bronchitis	5 (10.0)	5 (9.8)	8 (8.0)	4 (8.2)
Myalgia	4 (8.0)	4 (7.8)	9 (9.0)	4 (8.2)
Urinary Tract Infection	2 (4.0)	4 (7.8)	10 (10.0)	4 (8.2)
Alopecia	3 (6.0)	5 (9.8)	5 (5.0)	7 (14.3)
Muscle Spasms	6 (12.0)	4 (7.8)	4 (4.0)	6 (12.2)
Cough	7 (14.0)	3 (5.9)	6 (6.0)	3 (6.1)
Nausea	5 (10.0)	4 (7.8)	8 (8.0)	2 (4.1)
Rash	4 (8.0)	2 (3.9)	7 (7.0)	5 (10.2)
Osteoarthritis	3 (6.0)	4 (7.8)	7 (7.0)	2 (4.1)
Rhinitis	2 (4.0)	3 (5.9)	6 (6.0)	4 (8.2)
Gastroenteritis	4 (8.0)	4 (7.8)	3 (3.0)	4 (8.2)
Paraesthesia	5 (10.0)	4 (7.8)	4 (4.0)	2 (4.1)
Oral Herpes	3 (6.0)	2 (3.9)	4 (4.0)	5 (10.2)
Cataract	3 (6.0)	5 (9.8)	5 (5.0)	1 (2.0)
Neck Pain	2 (4.0)	4 (7.8)	6 (6.0)	1 (2.0)
Abdominal Pain Upper	3 (6.0)	4 (7.8)	3 (3.0)	3 (6.1)
Insomnia	4 (8.0)	4 (7.8)	4 (4.0)	1 (2.0)
Fall	2 (4.0)	2 (3.9)	7 (7.0)	2 (4.1)
Asthenia	5 (10.0)	0 (0.0)	5 (5.0)	3 (6.1)

Source: Adapted from WA28119 CSR Table 39 and Reviewer analysis JReview using terms AEDECOD, TRT01A

AEs were graded on a five-point intensity scale according to NCI CTCAE v4.0. There were no Grade 5 AEs (fatalities) during Part 1 of the study. Five patients experienced Grade 4 AEs including 1 patient with neutropenia (TCZ QW), 1 patient with pulmonary embolism (TCZ QW), 1 patient with thrombotic stroke (TCZ Q2W), 1 patient with arthralgia (PBO+26 wk), and 1 patient who experienced cardiac failure, elevated liver

enyzmes, hypokalemia, and renal impairment (PBO+52 wk). In the CSR, the Applicant has included a correction that the patient with neutropenia (253733/10942) actually had Grade 3 neutropenia, rather than Grade 4. The proportions of patients with Grade 3 AEs in each treatment group were similar (PBO+26 wk: 22.0%, PBO+52 wk: 25.4%, TCZ QW: 25%, and TCZ Q2W: 24.5%). The most frequently reported Grade 3 AEs include hypertension (3 patients in TCZ QW, 1 patient each PBO+26 wk, PBO+52 wk, and TCZ Q2W), temporal arteritis (1 patient in each treatment group), and herpes zoster (2 PBO+52 wk, 1 TCZ QW).

AEs observed in Study WA28119 occurring in a greater proportion of patients in the TCZ treatment groups as compared to the placebo treatment groups include hypertension and urinary tract infection. These are labeled adverse reactions. In the TCZ Q2W group, a smaller group exposed to less cumulative TCZ, oedema peripheral, dizziness, alopecia, rash, rhinitis, and oral herpes, were also reported by a greater number of patients as compared to the other treatment groups. Dizziness, rash, oral herpes simplex, and edema peripheral are labeled adverse reactions. Differences between treatment groups for these AEs were based on differences in 1-2 patients. Other reported AEs were generally balanced across the treatment groups. The observed common AEs are consistent with the known safety profile of TCZ. Overall rates of AEs were higher in the TCZ groups (872 and 948 events per 100 PY for TCZ QW and TCZ Q2W, respectively) in WA28119 than in the LTE RA population (296 events per 100 PY). As previously noted, differences in AE rates between the GCA and RA populations may be related to differences in underlying disease, concomitant steroid doses and other concomitant medications, patient demographics, and/or other differences, as well as differences in exposure and follow-up.

7.4.2 Laboratory Findings

Hematology
Decreases from baseline were observed in mean and median neutrophil and platelet counts (means presented in Table 22). Decreases occurred after the first TCZ dose and stabilized by Week 24. A greater proportion of patients in the TCZ QW group had a shift in neutrophil count from high/normal to low (49.0%) as compared to the TCZ Q2W (34.7%), PBO+52 wk (5.9%), and PBO+26 wk (2.0%) groups. Markedly low neutrophil counts (<1.5 x 10^9/L and a ≥20% change from baseline) were observed in 21 (21.0%) patients in the TCZ QW treatment group, 8 (16.0%) patients in TCZ Q2W, and 1 (2.0%) patient in each of the placebo treatment groups. Markedly low neutrophil counts were most frequently reported at Weeks 32, 40, and 48 according to this reviewer's analysis.

(b) (4)

Neutropenia/neutrophil count decreased was reported as an AE in 4 patients in the TCZ QW group and 2 patients in the TCZ Q2W group. None of the events were serious. One patient in the TCZ QW group withdrew from the study due to neutropenia. An

additional 2 patients in the TCZ QW group had study treatment interrupted or dose modification due to neutropenia. There was no association between Grade 3 or 4 events of neutropenia and serious infections.

Post baseline thrombocytopenia was observed in 1 (2.0%) patient in the PBO+52 wk group, 7 (7.0%) patients in the TCZ QW, and 5 (10.2%) patients in the TCZ Q2W groups. All events of thrombocytopenia were Grade 0 or 1 events. Mean decreases in platelet counts were 78.8 x 10^9/L and 58.8 x 10^9/L in the TCZ QW and TCZ Q2W treatment groups respectively, as compared to 6.7 x 10^9/L and 12.5 x 10^9/L in the PBO+26 wk and PBO+52 wk groups, respectively (Table 22). Markedly low platelet counts (<100 x 10^9/L and ≥ 30% change from baseline) occurred as a single occurrence in 1 patient (platelet count 87.7 x 10^9/L) in the TCZ QW group at an unscheduled visit on study day 76. This patient had a non-serious event of vaginal hemorrhage on study day 71. Thrombocytopenia/platelet count decreased was reported as a Grade 1 AE in 2 patients in the TCZ Q2W group; one of the patients had dose interruption due to platelet count decreased and ALT increased. There was no associated bleeding event in either patient.

Neutropenia was observed with greater frequency and severity in the TCZ groups as compared to the placebo treatment groups, and with greater frequency and severity in the TCZ QW as compared to the Q2W group consistent with a dose dependent effect. Thrombocytopenia was more frequently observed in the TCZ treatment groups as well, and with a greater mean decrease in platelets in the TCZ QW group, also consistent with a dose dependent effect.

Table 22: Mean values and changes from baseline in selected laboratory parameters at Week 52

	PBO+26wk N = 50	PBO+52wk N = 51	TCZ QW N = 100	TCZ Q2W N = 49
Hematology				
White Blood Cells, n	41	43	86	40
Mean count, x 10^9/L	8.1	7.7	5.4	5.6
Mean change, x 10^9/L	-2.2	-2.7	-5.6	-5.2
Neutrophils, n	41	42	86	40
Mean count, x 10^9/L	5.6	5.2	3.1	3.3
Mean change, x 10^9/L	-2.0	-2.3	-5.1	-4.5
Hemoglobin, n	41	43	86	40
Mean count, g/L	131.7	134.3	141.0	141.2
Mean change, g/L	0.1	0.6	8.6	5.3
Platelets, n	41	43	85	40
Mean count, x 10^9/L	288.6	284.8	212.2	208.2
Mean change, x 10^9/L	-6.7	-12.5	-78.8	-58.8
Chemistry				
Albumin, n	43	45	86	40
Mean value, g/L	40.8	41.3	43.3	43.1
Mean change, g/L	1.1	1.8	4.6	4.1
Alkaline phosphatase, n	44	45	86	41
Mean value, U/L	65.2	73.7	61.1	51.7
Mean change, U/L	1.8	7.5	-4.0	-13.9
ALT, n	43	45	86	41
Mean value, U/L	17.9	17.0	25.6	23.3
Mean change, U/L	-5.9	-19.5	4.2	0.8
AST, n	43	45	85	41
Mean value, U/L	18.1	18.8	24.3	23.4
Mean change, U/L	0.4	0.9	6.9	5.5
Total bilirubin , n	43	45	86	41
Mean value, umol/L	7.5	7.9	11.0	11.5
Mean change, umol/L	-1.4	-0.9	2.7	3.0
Creatinine, n	44	45	86	41
Mean value, umol/L	76.3	82.0	77.7	307.6
Mean change, umol/L	-1.9	-2.9	-2.4	228.3
Cholesterol (fasting), n	38	42	71	34
Mean value, mmol/L	5.7	5.4	6.2	6.1
Mean change, mmol/L	-0.5	-0.6	-0.1	-0.4
Cholesterol (nonfasting), n	6	3	15	6
Mean value, mmol/L	5.7	6.0	6.3	6.0
Mean change, mmol/L	0.2	-0.5	0.5	0.2
LDL (fasting), n	38	42	71	34
Mean value, mmol/L	3.3	3.0	3.5	3.5
Mean change, mmol/L	0.09	0.002	0.5	0.3
Hemoglobin A1c, n	44	45	86	40
Mean value, mmol/mol	42.9	42.1	36.9	37.4
Mean change, mmol/mol	-0.2	-1.9	-5.7	-6.5

Reviewer JMP analysis, ALB dataset (submitted in IR response dated 07April2017), using terms PARAM, AVAL, CHG, AVISIT, TRT01A, SAFFL='Y'

Chemistry
Changes from baseline were observed for liver (ALT, AST, bilirubin) and lipid (total cholesterol, LDL cholesterol) parameters. Small decreases in alkaline phosphatases and hemoglobin A1c, and increases in albumin were seen in the TCZ treatment groups. No clinically relevant changes over time were observed for other serum chemistry parameters.

Post-baseline elevations in transaminases were observed in a higher percentage of patients in the TCZ QW treatment group (ALT and AST elevations in 45.0% and 29.0%, respectively) than in the TCZ Q2W group (34.7% and 16.3%) and in the placebo groups (24-25.5% and 8.0-13.7%). Elevations in bilirubin occurred in a similar proportion of patients in the TCZ QW group (13.0%) and the TCZ Q2W group (14.3%), and occurred less frequently in the placebo groups (2.0% and 5.9% for the PBO+26 wk and PBO+52 wk groups, respectively). No patients met the laboratory criteria for Hy's law.

Mean and median ALT and AST values remained within the normal range through Part 1, although values were higher in the TCZ treatment groups as compared to the placebo treatment groups. At Week 52, the mean changes in AST and ALT values were higher in the TCZ groups as compared to placebo, and higher in the TCZ QW group as compared to the Q2W treatment group (Table 22). One post baseline Grade 3 elevated AST value was reported in 1 patient in the TCZ Q2W group (Week 1) and one Grade 2 elevated AST value was reported in 1 patient in the TCZ QW group (Week 1). Post baseline Grade 3 elevated ALT values were reported in 2 patients in the TCZ QW group (Week 1 and Week 8), and 1 patient each in the TCZ Q2W (Week 1), and PBO + 52 wk (Week 1) treatment groups, while Grade 2 elevated ALT values were reported in 1 patient in the TCZ Q2W group (Week 1) and 1 patient in the TCZ QW group (Week 2, this patient had Grade 3 value at Week 1). Markedly high AST abnormalities (AST >80 U/L and ≥ 50% change from baseline) were reported in 3 (3%) patients in the TCZ QW group and 2 (4%) patients in the TCZ Q2W group. Markedly high ALT abnormalities (ALT > 110 U/L and ≥ 50% change from baseline) were reported in 1 (2%) patient in the PBO+26 wk group, 14 (14%) patients in the TCZ QW group, and 3 (6%) patients in the TCZ Q2W group. (b) (4) AST ≥ 3x ULN was observed in 2 patients in the TCZ Q2W group (baseline, Week 1) and 1 patient in the TCZ QW group (Week 1); AST values were subsequently normal in all 3 patients. ALT values ≥3x ULN were reported in 4 patients in the TCZ QW, 2 in the TCZ Q2W, and 1 patient in the PBO+52 wk group. One patient in the TCZ QW had ALT≥3x ULN during screening only, therefore 3 patients in the TCZ QW group had post-baseline ALT ≥3x ULN.

Small increases in bilirubin were observed in both TCZ treatment groups at Week 52, while small decreases occurred in the placebo groups. Shifts from normal to high occurred in 1 patient in the PBO+26 wk group, 2 patients in the PBO+52 wk group, 13 patients in the TCZ QW group, and 6 patients in the TCZ Q2W group. Shifts from

normal to high occurred throughout the 52 week study period. Most were Grade 1, however there were 5 patients with Grade 2 elevated bilirubin levels (4 TCZ QW, 1 TCZ Q2W). A markedly high bilirubin level (>34 µmol/L and a ≥75% change from baseline) was reported in 1 patient in the TCZ QW group.

Seventeen patients experienced adverse events of alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, or transaminases increased, including 2 patients in the PBO+26 wk group, 2 in the PBO+52 wk group, 11 in the TCZ QW group, and 2 in the TCZ Q2W groups. One AE (hepatic enzyme increased) was reported as serious (PBO+52 wk) and AEs led to drug interruption in 6 patients (1 PBO+52 wk, 4 TCZ QW, 1 TCZ Q2W).

A dose dependent effect of TCZ on liver enzymes was observed. Mean changes in AST and ALT values at Week 52 were higher in the TCZ QW group as compared to the TCZ Q2W group and placebo groups. Markedly abnormal ALT results occurred in a greater proportion of patients receiving TCZ QW, while a similar proportion of patients in each of the TCZ groups reported Grade 2, Grade 3, and markedly abnormal AST results. Mean bilirubin levels were similar in both TCZ treatment groups. AEs of abnormal liver enzymes and AEs leading to drug interruption were more frequently reported in the TCZ QW group as compared to the TCZ Q2W and placebo groups. The proportions of patients in the TCZ QW and TCZ Q2W groups with AST and ALT values ≥3xULN were similar to that observed in rheumatoid arthritis described in the USPI.

Mean and median values for total cholesterol and LDL cholesterol at Week 52 were higher in the TCZ than in the placebo groups. Shifts from normal to high total cholesterol values occurred in 1 patient in each of the placebo groups, 11 (11%) patients in the TCZ QW group, and 7 (14%) patients in the TCZ Q2W group. Shifts from normal/low to high LDL values occurred in 2 (3.9-4%) patients in each of the placebo groups, 10 (10%) patients in the TCZ QW group, and 4 (8.2%) patients in the TCZ Q2W group. Markedly abnormal total cholesterol levels (>18.3 mmol/L and ≥30% increase) were reported in 3 patients in the TCZ QW group, 2 patients each in the TCZ Q2W and PBO+52 wk treatment groups, and 1 patient in the PBO+26 wk group. Markedly abnormal LDL values (>5.4 mmol/L and ≥30% increase) were reported in 3 patients in the TCZ QW and 1 patient in each of the TCZ Q2W and PBO+26 wk groups.

The majority of cholesterol studies were fasting values as shown in Table 22. Differences in fasting status at the time of laboratory testing may influence interpretation. Small decreases from baseline in total cholesterol were seen in those patients who had fasting cholesterol levels performed, while increases were seen in those patients with non-fasting samples. Small increases in LDL from baseline were observed, greater in the TCZ treatment groups than the placebo groups. Change from baseline was generally lower across the treatment groups when fasting LDL cholesterol was reported. Further, interpretation of cholesterol values may be limited by use of lipid lowering therapy. The proportion of patients receiving lipid lowering treatments was generally similar across the treatment groups (PBO+26 wk: 26.0%, PBO+52 wk: 33.3%,

TCZ QW: 32.0%, and TCZ Q2W: 30.6%). Lipid lowering therapy was initiated during the study in 1 (2.0%) patient in the PBO+26 wk group, 5 patients in each of the PBO+52 wk (9.8%) and TCZ Q2W (10.2%), and 11 (11.0%) patients in the TCZ QW treatment group.

Small elevations in mean cholesterol were observed in the TCZ treatment groups, with a greater proportion of patients shifting from normal to high total and LDL cholesterol values in the TCZ groups as compared to the placebo groups. Interpretations of change in cholesterol values are limited by differences in fasting status and initiation of lipid lowering therapy. While definitive conclusions cannot be drawn, lipid changes were generally consistent with those seen in RA.

7.4.3 Vital Signs

Vital signs assessments included pulse, temperature, and systolic and diastolic blood pressure (after patient supine for at least 5 minutes). Body weight was measured at baseline, Weeks 12, 24, and 52 and BMI was calculated at these timepoints.

No clinically relevant mean changes from baseline to Week 52 were observed for any vital sign parameter. Mean, median, and maximum temperatures were similar across treatment groups according to this reviewer's analysis. Median change in weight was somewhat lower in the PBO+26 wk treatment group (1.2 kg) as compared to the other treatment groups (2.65-2.8 kg). Minimum and maximum systolic and diastolic blood pressures were generally similar across treatment groups. Mean change from baseline in systolic blood pressure was small and ranged from -5.30 mm Hg in the PBO+26 wk group to -1.13 mm Hg in the TCZ QW treatment group. Mean change from baseline in diastolic blood pressure was also small; the greatest mean change at Week 52 was -2.16 in PBO+26 wk group.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed at baseline and at unscheduled visits as necessary through the study. Eighty patients had abnormal baseline ECGs, 4 of which were considered clinically significant (2 PBO+52 wk, 1 TCZ QW, and 1 TCZ Q2W). The patient in the TCZ QW treatment group with a clinically significant abnormal ECG at baseline experienced adverse events of hypertension and blood pressure increased. Other patients with clinically significant abnormal baseline ECGs did not experience relevant adverse events.

Fifteen patients (5 PBO+26 wk, 2 PBO+52 wk, 4 TCZ QW, 3 TCZ Q2W, 1 who did not receive study treatment in Part 1) had an ECG performed at times other than baseline. Of these, 4 of the 5 patients with abnormal ECGs were in the PBO+26 wk treatment group, while 1 patient was in the TCZ Q2W treatment group. None of the abnormal ECGs were reported to be clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were included in the submission.

7.4.6 Immunogenicity

Immunogenicity was assessed at baseline, Week 8, Week 24, Week 36, and at completion of the double blind period at Week 52. For patients who withdrew from the study or discontinued TCZ treatment because of anaphylaxis or hypersensitivity reactions (serious or non-serious), a sample for anti-TCZ antibodies was obtained at the time of the event and at least 8 weeks after the last dose of study drug. In patients who interrupted TCZ treatment for more than 4 weeks in either Part 1 or Part 2, a pre-dose sample for anti-TCZ antibodies was obtained prior to resumption of study medication. All samples were tested using a screening assay; positive tests were analyzed by a confirmation assay. If the confirmation assay was positive, a neutralizing assay to test ADA's neutralizing potential and an IgE assay to verify if the detected ADA were of the IgE isotype, were performed.

At baseline, 13 of 245 patients with ADA samples had positive screening ADA assays; 6 of these were confirmed positive (Table 23). None of the 6 patients with confirmed ADA at baseline had neutralizing potential, nor were these of IgE isotype.

Two hundred and thirty seven patients were evaluable for ADA, defined as a patient with a screening assay result at baseline, at least one post-baseline sample and who has received at least one dose of study treatment (active drug or placebo). Of these patients, 11 had confirmed ADA, 3 patients had ADA at baseline, 2 patients had ADA at baseline and post-baseline assessments, and 6 patients had confirmed ADA post-baseline. Of the patients who developed confirmed ADA post-baseline, 3 received TCZ Q2W, and 1 patient each received TCZ QW, PBO+26 wk, and PBO+52 wk. ADA displayed neutralizing potential in 6 patients in the TCZ treatment groups including 1 patient in the TCZ QW group and 5 patients who received TCZ Q2W. Two of the patients in the TCZ Q2W group who had non-neutralizing ADA at baseline, had confirmed ADA with neutralizing potential post-baseline, while three patients with neutralizing ADA did not display ADA at baseline. None of the ADA in the placebo treatment groups had neutralizing potential. None of the ADA were of the IgE isotype.

While the Applicant has included only "treatment-induced ADA" in the analysis in the clinical study report, Reviewer analysis included the two patients with baseline and post-baseline ADA to evaluate whether the change in neutralizing potential of the ADA in these patients is relevant to clinical and PK measures.

Table 23: Immunogenicity through Week 52

	PBO+26wk N = 50 n (%)		PBO+52wk N = 51 n (%)		TCZ QW N = 100 n (%)		TCZ Q2W N = 49 n (%)	
Baseline evaluable patients	50 (100.0)		49 (96.1)		99 (99.0)		47 (95.9)	
Baseline	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Confirmation assay	0	0	1	1	1	5	4	1
Neutralizing Ab	0		0		0		0	
ADA of IgE isotype	0		0		0		0	
Post baseline evaluable patients	49 (98.0)		47 (92.2)		95 (95.0)		46 (93.9)	
Post baseline confirmation assay	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Week 8	0	1	0	1	0	5	1	2
Week 24	0	0	0	2	1	3	3	1
Week 36	1	0	0	2	0	5	2	1
Week 52	0	0	1	1	0	4	1	1
Post baseline confirmation positive at any time	1		1		1		5*	
Post baseline neutralizing Ab	0		0		1		5	
Post baseline ADA of IgE isotype	0		0		0		0	

*2 patients (255213-10023/253730-11041) with confirmed ADA at baseline and post-baseline
Reviewer analysis in JMP AIM database using terms PARAM, LBSTRESC, VISIT, TRT01A, USUBJ

ADA were not observed in patients who experienced hypersensitivity (1 patient each in PBO+26 wk, PBO+52 wk, and TCZ Q2W), clinically significant hypersensitivity (2 patients in TCZ Q2W), nor in 1 patient (TCZ Q2W) who met Sampson's criteria for anaphylaxis. Nine patients withdrew due to insufficient therapeutic response; of these, only one patient (TCZ QW) had a confirmed ADA without neutralizing potential that was present at baseline and not present at post-baseline assessments. No other patients with insufficient therapeutic response had ADA. Of the 19 patients who reported injection site reactions, 1 patient (TCZ Q2W) had a positive screening ADA assay, but negative confirmatory testing. The two patients with non-neutralizing antibodies at baseline and neutralizing antibodies post-baseline did not experience insufficient therapeutic response, hypersensitivity, anaphylaxis, or ISR. None of the 4 patients who developed treatment-induced ADA after TCZ exposure became positive after dose interruptions during the study.

Assessment of TCZ concentrations in the 6 patients who had neutralizing antibodies showed decreased TCZ concentrations in 1 patient receiving TCZ Q2W. Similar trends for decreased TCZ concentrations at or subsequent to the visits at which neutralizing antibodies were observed were not seen in other patients.

There does not appear to be a relationship between the presence of ADA and development of hypersensitivity, anaphylaxis, insufficient therapeutic response, or ISR. Only patients exposed to tocilizumab developed neutralizing antibodies. However, in the small numbers of patients with neutralizing antibodies, there was no consistent decrease in tocilizumab concentrations. ADA antibodies and neutralizing antibodies were observed in 0.8% and 0.8%, respectively, of RA patients receiving SC TCZ QW in Study WA22762 and 1.6% and 1.4%, respectively, of patients receiving TCZ SC Q2W in Study NA25220. In WA28119, 2.5% of patients developed ADA (negative at baseline, positive post-baseline), and 2.5% of patients developed neutralizing antibodies. ADA Ab and neutralizing Ab were more frequently observed in patients in the TCZ Q2W treatment group, however this is based on a small number of patients. Differences in the proportion of patients developing neutralizing antibodies as compared to the RA population may be related to the concomitant use of DMARDs in the RA studies. Overall, the incidence of immunogenicity is low.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As discussed above, the overall proportion of patients who experienced SAEs and AEs leading to discontinuation were similar in the TCZ QW and TCZ Q2W groups. SAEs and AEs leading to discontinuation within the Infections and Infestations SOC occurred in more patients in the TCZ QW treatment group. The overall numbers of patients with infectious AEs were similar between the two dose groups; however, more patients experienced serious infections in the TCZ QW group. Opportunistic infections were rare during Part 1 of the study, reported in only a single patient in the TCZ Q2W group. Common AEs were reported in similar proportions of patients in each treatment group. Nasopharyngitis, urinary tract infection, and fall were more frequently reported by patients in the TCZ QW treatment group as compared to the TCZ Q2W and placebo treatment groups (Table 21). Overall, treatment with TCZ QW does not appear to pose an excessive additional risk for AEs as compared to treatment with TCZ Q2W in patients with GCA. The safety and immunogenicity were similar between the two TCZ dosing regimens and consistent with the established safety profile for TCZ in RA except for an overall higher incidence of infections in GCA patients. A greater proportion of patients experienced serious infections in the TCZ QW compared to TCZ Q2W treatment group.

7.5.2 Time Dependency for Adverse Events

The incidence of AEs is presented for the 52 week controlled portion of the study in section 7.3 Major Safety Results and 7.4 Supportive Safety Results. In the placebo treatment groups, AEs within the Infections and Infestations SOC increased over the 52 week period. In the PBO+52 wk treatment group, AEs within the Gastrointestinal Disorders SOC were also more frequently reported from study day 256-372, however, these were least frequently reported in the period before from study day 169-256. SAEs, AESI, and AEs leading to withdrawal of TCZ/placebo treatment remained generally stable over time. The relatively stable incidence of AEs over time suggests that longer exposure does not confer increased risk of cumulative toxicity, at least as observed over the 52 week period of study.

7.5.3 Drug-Demographic Interactions

Safety analyses based on demographic characteristics were not conducted by the Applicant. The discussion below is based on Reviewer analysis of the AAE and ASL datasets using JMP.

SAEs
Of the 46 patients who reported SAEs, the majority were female (31, 67.4%), Caucasian (45, 97.8%), and non Hispanic or Latino (44, 95.7%) reflecting the demographics of the enrolled patients of whom 75% were female, nearly 97% were Caucasian, and 95.6% identified as non Hispanic or Latino. Fewer patients in the TCZ QW group experiencing SAEs were female (53.3%), as compared to the TCZ Q2W (71.4%), PBO+26 wk (63.6%), and PBO+52 wk (84.6%) treatment groups, however differences are due to small numbers of patients. There were no consistent patterns of SAEs by body weight group and treatment group; a greater proportion of < 60 kg patients in the TCZ Q2W and PBO+26 wk groups experienced SAEs, while in the 60-100 kg weight group, greater proportion of patients in the placebo groups reported SAEs as compared to the TCZ treatment groups.

The mean age of patients with SAEs was 71.0 years (SD 8.6) and the median age was 72.5 years. Patients in the PBO+52 wk group who experienced SAEs were younger with a mean age of 66.1 (SD 7.0), and median of 65 years, while the mean and median ages in the other treatment groups were similar.

AEs leading to discontinuation
Twenty-three patients reported AEs leading to blinded treatment discontinuation using variable “AEWITHFL”. Fifteen patients (65.2%) were female, 21 (91.3%) were Caucasian, and 21 (91.3%) were also non Hispanic or Latino. The mean and median ages of patients with AEs leading to discontinuation was 73.3 (SD 7.3) and 74, respectively. The distribution of sex, race, ethnicity, and age was generally similar across the treatment groups in which patients experienced AEs leading to discontinuation (PBO+26 wk, TCZ QW, and TCZ Q2W). A greater proportion of

patients in the highest body weight category, >100 kg, had AEs leading to blinded study treatment discontinuation (15.4%), as compared to the 60-100 kg (9.4%) and <60 kg (7.6%) weight groups. In the 60-100 kg weight group, greater proportions of patients in the TCZ treatment groups (12.5% and 12.9%) reported AEs leading to treatment discontinuation as compared to the PBO+26 wk group (9.1%) and PBO+52 wk (0), while in the <60 kg weight group, a greater proportion of patients in the PBO+26 wk group (14.3%) reported AEs leading to treatment discontinuation as compared to the TCZ treatment groups (7.4% for TCZ QW and 7.7% for TCZ Q2W). Conclusions are limited by the small numbers of patients in the >100 kg group and the relatively small number of events.

Using variable DISCDBR 'Adverse Event' and 'AEACN1 'Drug Withdrawn' identifies 15 patients who reported AEs leading to double blind treatment and 19 patients who reported AEs leading to blinded TCZ/placebo discontinuation, respectively. Analysis by sex, race, ethnicity, and age is generally similar as seen with AEWITHFL, though the PBO+26 wk had a similar mean age with an older median age, as compared to the TCZ treatment groups with both analyses.

AEs
Two hundred and forty patients reported 2198 TEAEs. One hundred and seventy nine patients (74.6%) were female, 235 (97.9%) were Caucasian, and 229 patients (95.4%) were non Hispanic or Latino; this was similar across the treatment groups. The proportions of patients reporting AEs were similar across body weight groups and treatment groups. The mean and median ages of patients reporting TEAEs were 69.0 (SD 8.2) and 70 years, respectively. Patients in the PBO+52 wk group who experienced AEs were slightly younger with a mean age of 67.4 (SD 7.7), and median of 68 years. The mean and median ages of the other treatment groups were similar.

Analysis of TEAEs, SAEs, and AEs leading to discontinuation by demographic subgroups, including body weight group, was similar to the safety profile of the overall study population. This analysis is limited by the small number of non-Caucasian and non-female patients enrolled in the study.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

No new data on drug interactions are included in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information regarding human carcinogenicity is included in this supplement.

7.6.2 Human Reproduction and Pregnancy Data

The Applicant previously submitted available human reproduction and pregnancy data as part of labeling updates to comply with Pregnancy and Lactation Labeling requirements during the review of BLA 125472/supplement 18, approved 23Sept2016. No new information is submitted with this supplement.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant submitted an initial pediatric study plan which was agreed upon by the Agency. The Applicant requested a full waiver of the requirement to submit a pediatric assessment for giant cell arteritis in the pediatric population. The justification for this waiver request is that GCA only occurs in adult populations and therefore, studies are impossible or highly impractical because the number of patients is so small or geographically dispersed. The proposed pediatric plan was reviewed at the FDA Pediatric Review Committee (PeRC) on 04Nov2015. The requested full waiver for pediatric studies is acceptable for GCA. Agreement on the pediatric study plan was acknowledged on 15Jan2016.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information regarding overdose, drug abuse potential, withdrawal and rebound is included in this supplement.

7.7 Additional Submissions / Safety Issues

Safety Update

A 90 day Safety Update that includes data through a clinical cut-off of 10Oct2016, was submitted on 17Feb2017. Two hundred and fifteen (215) patients entered Part 2 (44 PBO+26 wk, 46 PBO+52 wk, 85 TCZ QW, and 40 TCZ Q2W). Two deaths were reported during Part 2 including the fatal aortic dissection described in 7.3.3

Dropouts and/or Discontinuations, and the death of a patient with a history of coronary artery disease, diabetes, and hypertension, who received TCZ QW in Part 1 and again after Week 64, who experienced acute pancreatitis and acute myocardial infarction. One patient with genital tract tuberculosis discontinued the study. Rates of AEs by events per 100 patient years, were reported as “On TCZ” if the patient was on TCZ or had received within 14 days prior to onset of event, and otherwise reported as “Not on TCZ.” There was a higher rate of AEs, SAEs, infections, serious infections, ISR

in the On TCZ group as compared to the Not on TCZ in combined Parts 1 and 2. The types of AEs reported in Part 2 were similar to those observed during Part 1 of the study. Analysis of malignancies showed a higher rate per 100 PY in those "Never treated" with TCZ as compared to those ever treated with TCZ in Parts 1 and 2. Rates of myocardial infarction and serious bleeding were higher in the "Ever Treated" group, however, these were based on few events, while rates of stroke were similar between Never and Ever TCZ Treated groups.

The types of AEs reported in the safety update are consistent with the known safety profile of TCZ. No new safety signals are identified.

Study ML25676

The Applicant has submitted summary data from Study ML25676, a single center, randomized, double-blind, placebo-controlled study in 30 patients with GCA, diagnosed based on the 1990 ACR criteria, who were randomized 2:1 to treatment with IV tocilizumab 8 mg/kg or placebo every 4 weeks for 52 weeks. Both treatment groups also received oral prednisolone starting at a dose of 1 mg/kg/day and tapering by a standardized schedule. Adverse events were reported in a similar proportion of patients in each treatment group (TCZ: 75%; PBO: 70%). A greater proportion of patients in the PBO group (50%) experienced SAEs than the TCZ group (35%) (Table 24). While detailed data including preferred terms for all events are not available, the publication describes select SAEs. Cardiovascular SAEs including percutaneous coronary intervention with fatal myocardial infarction, and a patient who experienced syncope, occurred in the PBO group. In the TCZ treatment group, 1 patient had severe headache with tinnitus. GI perforations were reported in 1 TCZ-treated patient with perforation of a prepyloric ulcer and in 1 PBO-treated patient with previously undiagnosed diverticulitis who experienced a sigmoid perforation. One patient in the TCZ group experienced Stevens-Johnson syndrome 3 days after the third infusion. Other AEs reported in the publication in single patients in the TCZ treatment group included hepatopathy due to an undefined viral infection, gastrointestinal bleeding requiring endoscopy, severe psychosis, and eye infection due to Moraxella catarrhalis and herpes, while events in single patients in the placebo group included steroid-induced myopathy, hyperglycemia, severe back pain, and lumbar fracture requiring vertebroplasty.

Table 24: AEs by Treatment Group, Study ML25676

	Tocilizumab plus prednisolone (N=20)	Placebo plus prednisolone (N=10)
Number of adverse events	26 (15 patients)	23 (7 patients)
Serious adverse events	7 (7 patients)	10 (5 patients)
Cardiovascular disease	1	5 (1 cardiovascular-related death)
Gastrointestinal disease	4	1
Osteoporotic fracture	1	3
Musculoskeletal disease	5	8
Glucocorticoid-related hyperglycaemia and myopathia	3	3
Infectious disease	10	1
Skin disease	1	2
Cystic lesion mamma	1	0

Source Villiger et al, 2016. Table 3

Conclusions regarding the safety from Study ML25676 are based on the review of summary data presented in the publication by Villiger et al. The types of observed AEs appear consistent with the known safety profiles of TCZ and corticosteroids. While it is stated that there were no infusion-related AEs, the event of Stevens-Johnson syndrome that occurred following an infusion is suggestive of an infusion-related AE. Hypersensitivity reactions, including anaphylaxis and death, are labeled Warnings and Precautions of Actemra treatment. A greater proportion of patients in both treatment groups in Study ML25676 reported SAEs as compared to Study WA28119. Differences in patient populations, study design, and steroid taper limit direct comparison between the studies of IV and SC TCZ treatment in GCA.

8 Postmarket Experience

Since the approval of SC tocilizumab on October 21, 2013, there have been no safety-related labeling revisions. Periodic review of the post-marketing safety data (Periodic Safety Update Report for Actemra/tocilizumab, most recent report covering period 11 April2016 to 10 Oct2016) has not identified any new safety signals. On 12June2013, a Drug Safety Report on inflammatory eye disease (IED) was submitted upon agency request and reviewed by the Division of Pharmacovigilance (DPV) with concurrence that there was no evidence for an actionable safety signal for IED with tocilizumab. On 18Aug2016, a new Tracked Safety Issue for GI perforations associated with the use of tocilizumab was created in response to a literature report.

9 Appendices

9.1 Literature Review/References

Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatol 2010;49(8):1594-7.

Dasgupta B and Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. Br J Rheumatol 1990;29(6):456–8.

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Hunder GG, Block DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33(8):1122-8.

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Mukhtyar C, Guillevin L, Cid M, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68(3):318-323.

Roche NE, Fulbright JW, Wagner AD, et al. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum 1993;36(9):1286-94.

Weyand CM, Fulbright JW, Hunder GG, et al. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. Arthritis Rheum 2000;43(5):1041-8.

Weyand CM, Hicok KC, Hunder GG, et al. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Ann Intern Med 1994;121(7):484-91.

Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomized, double-blind, placebo-controlled trial. Lancet 2016; 387(10031):1921-7.

Yates, M., Loke, Y.K., Watts, R.A. et al. Prednisolone combined with adjunctive immunosuppression is not superior to prednisolone alone in terms of efficacy and safety in giant cell arteritis: meta-analysis. Clin Rheumatol 2014;33(2):227-36.

9.2 Labeling Recommendations

- **Proprietary name**

The trade name for tocilizumab, Actemra, has previously been reviewed and approved.

- **Physician labeling**

At the time of this review, labeling discussions are ongoing, however, the following general recommendations are suggested:

Table 25: Labeling Recommendations

Label Section	General Recommendations
Highlights, 2.2	Addition of text describing Actemra 162 mg SC every other week to be used in combination with a tapering course of glucocorticoids in some patients based on clinical considerations
[redacted] (b) (4)	
2.2 Giant Cell Arteritis	Add bullet stating intravenous administration is not approved for GCA to align with information for SC Actemra under Sections 2.3 and 2.4
	[redacted] (b) (4)
	Add statement that interruption of dosing may be needed for management of dose-related laboratory abnormalities to align with other indications as well as Section 2.8
[redacted] (b) (4)	
6.3 Clinical Trials Experience	Given that the overall safety profile is similar to that in RA, except for serious infections, add statement that overall higher incidence of infections in GCA patients with rates of infections and serious infections observed in each treatment group
	[redacted] (b) (4)
14.3 Giant Cell Arteritis	Description of Study WA28119 design edited to align with description of studies in 14.2. [redacted] (b) (4)
14.3 Giant Cell Arteriti [redacted] (b) (4)	Remove [redacted] (b) (4) from the definition of primary endpoint, modify to state sustained remission from Week 12 to Week 52 and adherence to protocol-defined prednisone taper.

	Clarify definition of sustained remission with description of components
	(b) (4)
14.3 Giant Cell Arteriti (b) (4)	(b) (4)
	Add text to describe annual cumulative prednisone dose at Week 52 to adjust for study follow-up time
14.3 Giant Cell Arteritis/Table (b) (4) Efficacy Results	(b) (4) Include components of sustained remission.
	(b) (4)

- **Carton and immediate container labels (if problems are noted)**

Carton and container labels are already approved, and no changes are proposed or warranted.

- **Patient labeling/Medication guide (if considered or required)**

The Patient labeling/Medication guide was approved as a component of REMS with the original BLA applications. On August 18, 2015, the REMS for Actemra (BLA 125276 and 125472) was released based on the confirmation that there has been at least one complete assessment, the REMS goals were met, and there were no identified or emerging safety issues that require continued or new communication within the subsequent 6 months. Proposed changes to the Medication Guide include the addition of giant cell arteritis in the description of conditions Actemra is used to treat, in the guidance regarding monitoring for changes in laboratory tests, and in the information about how Actemra will be administered for specific indications. The remainder of the Medication Guide, including the safety information, is unchanged.

9.3 Advisory Committee Meeting

No advisory committee was convened for this supplemental BLA.

Appendix 1: Prednisone Tapering Schedules

Prednisone Short Taper (26 weeks N=200)							Prednisone Long Taper (52 weeks N=50)						
Taper Week	mg/d	5mg	2.5mg	1mg	Placebo		Taper Week	mg/d	5mg	2.5mg	1mg	Placebo	
1	60	Open label supplied by Sponsor Patient starts at any of these incremental dosages				OPEN LABEL	1	60	Open label supplied by Sponsor Patient starts at any of these incremental dosages				OPEN LABEL
2	50						2	50					
3	40						3	40					
4	35						4	35					
5	30						5	30					
6	25						6	25					
7	20						7	20					
8	15	3			1	BLINDED	8	17.5	3	1			BLINDED
9	12.5	2	1		1		9	17.5	3	1			
10	12.5	2	1				10	15	3				
11	10	2			1		11	15	3				
12	9	1		4			12	12.5	2	1		2	
13	8	1		3			13	10	2			2	
14	7	1		2			14	10	2			1	
15	6	1		1			15	10	2				
16	6	1		1			16	10	2				
17	5	1			4		17	9	1		4		
18	5	1			4		18	9	1		4		
19	4			4	1		19	9	1		4		
20	4			4	1		20	9	1		4		
21	3			3	1		21	8	1		3		
22	3			3	1		22	8	1		3		
23	2			2	2		23	8	1		3		
24	2			2	2		24	8	1		3		
25	1			1	2		25	7	1		2		
26	1			1	2		26	7	1		2		
27	0				3		27	7	1		2		
28	0				3		28	7	1		2		
29	0				2		29	6	1		1		
30	0				2		30	6	1		1		
31	0				2		31	6	1		1		
32	0				2		32	6	1		1		
33	0				1		33	5	1				
34	0				1		34	5	1				
35	0				1		35	5	1				
36	0				1		36	5	1				
37	0				4		37	4			4		
38	0				4		38	4			4		
39	0				4		39	4			4		
40	0				4		40	4			4		
41	0				3		41	3			3		
42	0				3		42	3			3		
43	0				3		43	3			3		
44	0				3		44	3			3		
45	0				2		45	2			2		
46	0				2		46	2			2		
47	0				2		47	2			2		
48	0				2		48	2			2		
49	0				1		49	1			1		
50	0				1		50	1			1		
51	0				1		51	1			1		
52	0				1		52	1			1		
53	0				1		53	0				1	
54	0				1		54	0				1	
55	0				1		55	0				1	
56	0				1		56	0				1	
57	0				1		57	0				1	
58	0				1		58	0				1	

Source: Protocol WA28119 (Version 4)

Appendix 2: Schedule of Assessments

Assessment	Screening up to 42 days	BS	Study Week (±3 days)[a]									Study Week (± 7 days)[a]							Early WD[b]	FU Wk 4 (± 3 days)	FU Wk 8 (± 3 days)	Unsch Assess
			1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52				
Informed consent	X																					
Patient randomization		x																				
Demographics	X																					
Medical history	X																					
Review of inclusion and exclusion criteria	X	x																				
Rheumatoid factor, protein electrophoresis, HBsAg, and HCV serology	X																					
TB screening[c]	X																					
Physical exam[d] (including height at screening only)	X																	x	x			x
Vital signs[e]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
Body weight	X							x			x							x	x			x
SC injection at study site[f]		x	x	x	x				x[g]									x				
Study drug dispensed to patient *(contact IxRS for drug assignment)*		x[h]	x h	x h	x	x	x	x	x	x	x	x	x	x	x	x	x					
Concomitant medications	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Electrocardiogram	X																					x
Chest X-ray[i]	X																					x
High-sensitivity CRP	X	x	x	x	X	x	X	x	X	X	x	X	X	x	x	X	x	x	x			X
ESR	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
Clinical Assessor's GCA assessment S&S[j]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
Patient GA (VAS)[k]		x						x			x			x			x	x	x			
EQ-5D[k]		x						x			x			x			x	x	x			x
SF-36[k]		x						x			x			x			x	x	x			
FACIT-Fatigue[k]		x									x						x	x	x			
Adverse events[l]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology (CBC)	X	x	x				x		x		x		x		x		x	x	x			x
Serum chemistry	X	x					x		x		x		x		x		x	x	x			x
Liver profile[m]	X	x	x				x		x		x		x		x		x	x	x			x
Lipid panel and HbA1c[n]		x	x				x		x		x		x		x		x	x	x			x
Urinalysis[o]	X																	x				x
Anti-TCZ antibodies sample[p,q,r]		x					x				x			x				x	x[q]		x	x
Serum sample for TCZ concentration[p,q,r,s,t] sIL-6R and IL-6 sample[p,q,r]		x	x	x	x		x		x		x			x			x	x	x[q]		x (except IL-6)	x
RNA blood sample		X				X		X			X						X		X			X
Serum samples for biomarkers		x				X		x			x						X		X			X
DNA sample for biomarkers (RCR;O)		x																				

Source: Protocol WA28119 (Version 4)

Appendix 3: Adverse events leading to discontinuation of blinded treatment (Safety Population)

System organ class Preferred term	PBO+26wk N = 50 n (%)	PBO+52wk N = 51 n (%)	TCZ QW N = 100 n (%)	TCZ Q2W N = 49 n (%)
Number of patients with AEs leading to study treatment discontinuation	**6 (12.0)**	**0**	**11 (11.0)**	**6 (12.2)**
Infections and Infestations	**1 (2.0)**	**0**	**5 (5.0)**	**1 (2.0)**
Gastroenteritis	0	0	1 (1.0)	0
Pneumonia	1[2] (2.0)	0	1[2] (1.0)	0
Cellulitis	0	0	0	1[2] (1.0)
Chronic Sinusitis	0	0	1[2] (1.0)	0
Herpes Zoster	0	0	1 (1.0)	0
Pneumonia Haemophilus	0	0	1[1, 2] (1.0)	0
Sepsis	0	0	1 (1.0)	0
Musculoskeletal And Connective Tissue Disorders	**2 (4.0)**	**0**	**3 (3.0)**	**0**
Muscular Weakness	1[1] (2.0)	0	0	0
Myalgia	1 (2.0)	0	0	0
Osteoarthritis	0	0	1[1] (1.0)	0
Pain in Extremity	0	0	1 (1.0)	0
Spondylitis	0	0	1[1](1.0)	0
Vascular Disorders	**0**	**0**	**1 (1.0)**	**2 (4.1)**
Deep Vein Thrombosis	0	0	1[2] (1.0)	0
Dry Gangrene	0	0	0	1[2] (2.0)
Temporal Arteritis	0	0	0	1[1,2] (2.0)
Blood and lymphatic disorders	**0**	**0**	**2 (2.0)**	**0**
Anaemia	0	0	1 (1.0)	0
Leukocytosis	0	0	1 (1.0)	0
Neutropenia	0	0	1[1] (1.0)	0
Gastrointestinal disorders	**1 (2.0)**	**0**	**1 (1.0)**	**1 (2.0)**
Nausea	0	0	1 (1.0)	0
Sensitivity of Teeth	0	0	0	1 (2.0)
Stomatitis	1[2] (2.0)	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**1 (2.0)**	**0**	**1 (1.0)**	**0**
Breast cancer	1[1, 2] (2.0)	0	0	0
Marginal Zone Lymphoma	0	0	1 (1.0)	0
Respiratory, Thoracic And Mediastinal Disorders	**1 (2.0)**	**0**	**1 (1.0)**	**0**
Nasal inflammation	1[2] (2.0)	0	0	0
Pleural effusion	0	0	1[2] (1.0)	0
Eye Disorders	**0**	**0**	**0**	**1 (2.0)**
Optic Ischaemic Neuropathy	0	0	0	1[1] (2.0)
General Disorders and Administration Site Conditions	**0**	**0**	**1 (1.0)**	**0**

Oedema Peripheral	0	0	1 (1.0)	0
Immune System Disorders	**0**	**0**	**0**	**1 (2.0)**
Hypersensitivity	0	0	1 (1.0)[1,2]	0
Injury, Poisoning and Procedural Complications	**0**	**0**	**1 (1.0)**	**0**
Tendon Rupture	0	0	1 (1.0)[2]	0
Investigations	**0**	**0**	**1 (1.0)**	**0**
Blood Creatine Phosphokinase Increased	0	0	1 (1.0)[1]	0
Nervous System Disorders	**1 (2.0)**	**0**	**0**	**0**
Sciatica	1 (2.0)	0	0	0
Psychiatric Disorders	**0**	**0**	**1 (1.0)**	**0**
Anxiety	0	0	1 (1.0)	0
Skin and Subcutaneous Tissue Disorders	**1 (2.0)**	**0**	**0**	**0**
Rash	1 (2.0)[1]	0	0	0

[1] Led to study discontinuation
[2] SAE
Reviewer JMP analysis AAE dataset using terms: AEWITH='Y', USUBJID, AESOC, AEDECOD
Clinical Study Report pages 833-836

Appendix 4: Financial Disclosure Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: 125276/s112; 125472/s24

Submission Date(s): 11/23/2016; 11/22/2016

Applicant: Roche

Product: tocilizumab/Actemra

Reviewer: Rachel L. Glaser, MD

Date of Review: 03/10/2017

Covered Clinical Study (Name and/or Number): WA28119

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 526		
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): 2		
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: 2 Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in 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) n/a		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL GLASER
04/28/2017

NIKOLAY P NIKOLOV
04/28/2017
I concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125472/s24; 125276/s112 | **Applicant: Genentech, Inc** | **Stamp Date: November 22 and 23, 2016**

Drug Name: tocilizumab | **NDA/BLA Type: Priority Review**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			PLLR update completed with supplement 18/107
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Clinical and clinical pharmacology
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			In Clinical Overview page 51
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			X	505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				
14.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: WA28119 Study Title: A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in subjects with giant cell arteritis	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 251 Treatment Arms: • PBO QW + 26 wk prednisone taper • PBO QW + 52 wk prednisone taper • TCZ 162 mg QW + 26 wk prednisone taper • TCZ 162 mg QOW + 26 wk prednisone taper Location in submission: Module 5.3.5.1 \\cdsesub1\evsprod\bla125472\0116\m5\53-clin-stud-rep\535-rep-effic-safety-stud\giant-cell-arteritis\5351-stud-rep-contr\wa28119\csr-wa28119.pdf				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in subjects with giant cell arteritis Indication: Giant cell arteritis	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	15 of 76 centers were in North America. 4.8% of patients recruited were by USA centers
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	QT study conducted and reviewed in BLA 125276
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA Version 19.0
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			AESI were defined based on safety concerns for GCA population, clinical studies in RA, and safety profile of other biologics used to treat RA
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested, agreed PSP 01/15/2016
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?			X	This review was previously submitted on 01/29/2016 as part of sBLA-18
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	15 of 76 centers were in North America. 4.8% of patients recruited

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					were by USA centers
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None.**

Reviewing Medical Officer Date

Clinical Team Leader Date

U.S. FOOD & DRUG ADMINISTRATION

Received: November 22, 2016
PDUFA: May 22, 2017

sBLA 125472/24, 125276/112
Actemra (tocilizumab)
Giant Cell Arteritis

MO: Rachel L. Glaser, M.D.
CDTL: Nikolay P. Nikolov, M.D.
Filing/Planning Meeting
January 5, 2017

Executive Summary

Product: tocilizumab (IL-6 inhibitor)

Indication	Route	Dosing Regimen		Approval
RA	IV		4 mg/kg q4 wks, increase to 8 mg/kg q4 wks	08Jan 2010
	SC	< 100 kg	162 mg qowk, increase to qwk	21Oct 2013
		> 100 kg	162 mg qwk	
pJIA	IV	< 30 kg	10 mg/kg q 4 wks	29 April 2013
		≥ 30 kg	8 mg/kg q4 wks	
sJIA	IV	< 30 kg	12 mg/kg q 4 wks	15April 2011
		≥ 30 kg	8 mg/kg q4 wks	

Proposed Indication: Treatment of giant cell arteritis
Proposed dose: 162 mg SC qweek, in combination with a tapering course of GCs

Recommendations: Fileable as a priority sBLA (BTD)

2

Regulatory History

Date	Action	Notes
Jan 17, 2012	PIND Meeting	• Dose and POA not justified in GCA, POC study suggested • Recommended comparison steroid treatment group for entire controlled period • Investigators may become unblinded if aware of results of inflamm markers • Refine definition of refractory disease to ensure refractory population captured
Oct 19, 2012	IND submission	
Dec 5, 2012	SPA non-agreement	• Primary EP inadequate comparison as Group C undertreated. Advised to analyze comparison of proportion of patients with sustained remission between Groups A and D • Data from single trial to show efficacy in induction and maintenance of remission depends on robustness of data and support from 2° EPs • Definition of refractory patients may capture undertreated patients
Aug 21, 2015	SAP comments communicated	• Concerns re: primary EP may bias results in favor of TCZ • Noninferiority margin for 2° EP not justified • Definition of flare that incorporates inflamm markers
Sept 11, 2015	iPSP submitted	• Full waiver requested
Jan 15, 2016	Agreed PSP	
June 10, 2016	SAP comments communicated	• Primary EP is composite, evaluate supportive analyses of each component • Recommend assess superiority of TCZ+26 over PBO+52 as 2° EP
Aug 29, 2016	Pre-sBLA meeting	• Supportive analyses : symptomatic flare without ESR, CRP or steroid use • Evaluate differences between TCZ QW and Q2W and justify why differences meaningful • Evaluate potential impact of ADA on efficacy • Concerns raised with interpretability of CL uncontrolled data to inform long term dosing regimen in GCA
Aug 31, 2016	BTD Granted	

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FDA U.S. FOOD & DRUG ADMINISTRATION

Study WA28119

A Phase III, Multicenter, Randomized, Double-Blind Placebo-Controlled Study To Assess The Efficacy And Safety Of Tocilizumab In Subjects With Giant Cell Arteritis (GiACTA)

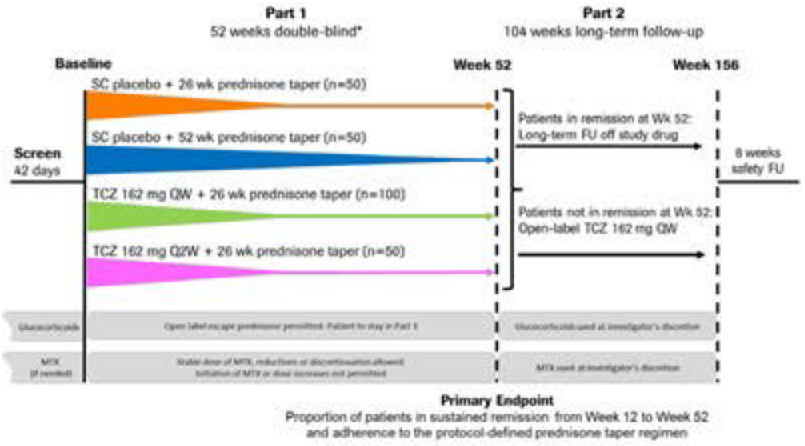
Study WA28119

- 156 wk MC, R, PC, DB, PG study to evaluate efficacy and safety of TCZ for GCA
  - Part 1: 52 wk DB
  - Part 2: 104 wk OLE
- Population: New onset and refractory GCA
- Treatment groups (randomized* 2:1:1:1):
  - Group A: 162 mg SC TCZ QW + 26-week prednisone taper regimen (TCZ QW)
  - Group B: 162 mg SC TCZ Q2W + 26-week prednisone taper regimen (TCZ Q2W)
  - Group C: SC PBO + 26-week prednisone taper regimen (PBO + 26)
  - Group D: SC PBO + 52-week prednisone taper regimen (PBO + 52)
- EPs:
  - Primary: Proportion of patients in sustained remission at Wk 52 in groups receiving TCZ (QW and Q2W) + 26 vs. PBO + 26
  - Key secondary: Proportion of patients in sustained remission at Wk 52 in groups receiving TCZ (QW and Q2W)+ 26 vs. PBO + 52
  - Secondary: Time to GCA flare, cumulative prednisone dose, patient global assessment, change in SF-36 summary scores

* Randomization stratified by baseline prednisone >30 mg/day or ≤30 mg/day

5

Study Scheme



6

Primary Endpoint Definitions

Proportion of GCA patients in sustained remission at Week 52 following induction and adherence to the protocol-defined prednisone taper regimen

- Remission was defined as the absence of flare and normalization of the CRP (<1 mg/dL)
- Induction of remission must occur within 12 weeks of randomization
- Sustained remission was defined as absence of flare following induction of remission up to the 52 week time point
  - Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or ESR ≥30 mm/hr attributable to GCA
- Patients had to follow protocol-defined prednisone taper regimen

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Eligibility

Inclusion Criteria

- Dx GCA
  - Cranial sx and/or sx of PMR
  - Elevated inflamm markers (ESR ≥50 mm/hr or CRP ≥2.4 mg/dL)
  - TA bx or imaging confirmation
- New onset or refractory GCA
  - New onset: dx ≤6 wks before baseline
  - Relapsing:
    - Dx >6 wks before baseline
    - Received prednisone ≥ 40 mg/day for ≥ 2 consecutive wks
    - Active GCA within 6 wks (clinical signs and symptoms and ESR ≥30 or CRP≥1)
  - Elevated inflamm markers not required if confirmed by positive biopsy within 6 weeks of baseline

Exclusion Criteria

- Major ischemic event unrelated to GCA w/in 12 wks
- Requirement for steroids for conditions other than GCA that may interfere with taper
- Use of chronic steroids for >4 years or inability to withdraw in opinion of investigator
- Receipt of > 100 mg daily IV methylpred within 6 weeks of baseline
- Active TB req treatment within 3 years
- Other specified biologics, DMARDs, cell-depleting therapy
- Infection, immunodef
- Serious uncontrolled concomitant CV, neuro, pulmonary, renal, hepatic, endo, psych, osteoporosis/malacia, glaucoma, cataracts, or GI dz
- Malignancy within 5 years
- h/o diverticulitis or chronic ulcerative lower GI dz
- Breastfeeding, males not willing to use effective contraception
- Pre-defined lab abnormalities

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Steroid taper and escape

- OL up to and inclusive of 20 mg/day
- Switched to double-blind for dosages below 20 mg to 0 mg
- Disease flare/unable to adhere to taper
  - OL escape prednisone 20 mg/day, followed by investigator defined schedule
  - Cont blinded TCZ or PBO SC injections for entire 52 weeks

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Primary Endpoint

Table 2 Proportion of Patients Achieving Sustained Remission at Week 52 (TCZ versus PBO QW + 26 wk) – ITT Population

	PBO QW + 26 Week Prednisone Taper N = 50	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
Responders	7 (14.0%)	56 (56.0%)	26 (53.1%)
Non-Responders [a]	43 (86.0%)	44 (44.0%)	23 (46.9%)
Unadjusted difference in response rates		42.00	39.06
99.5% CI		(18.00, 66.00)	(12.46, 65.66)
p-value (Cochran-Mantel-Haenszel) [b]		< 0.0001	< 0.0001

Patients were in sustained remission when they were responders from Week 12 to Week 52.

[a] Patients not adhering to the protocol-defined prednisone taper or who experienced more than one consecutive CRP elevation were classed as non-responders (details of responder derivation to be included in CSR).

[b] Stratification factor, starting prednisone dose (≤ 30 mg/day, >30 mg/day) was included in the model.

Source: t_ef_sum_IT

TCZ QW and TCZ Q2W superior to PBO + 26 week steroid taper

Supported by sensitivity analyses*

*tipping point, analysis excluding CRP<1 from defn of sustained remission, completers analysis, analysis of all subjects regardless of failure to adhere to taper regimen

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Key Secondary Endpoint

Table 4 Proportion of Patients Achieving Sustained Remission at Week 52 (TCZ versus PBO QW + 52 wk) – ITT Population

	PBO QW + 52 Week Prednisone Taper N = 51	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
Responders	9 (17.6%)	56 (56.0%)	26 (53.1%)
Non-Responders [a]	42 (82.4%)	44 (44.0%)	23 (46.9%)
Unadjusted difference in response rates		38.35	35.41
99.5% CI		(17.89, 58.81)	(10.41, 60.41)
p-value (Cochran-Mantel-Haenszel) [b]		< 0.0001	0.0002

Patients were in sustained remission when they were responders from Week 12 to Week 52.

[a] Patients not adhering to the protocol-defined prednisone taper or who experienced more than one consecutive CRP elevation were classed as non-responders (details of responder derivation to be included in CSR).

[b] Stratification factor, starting prednisone dose (≤ 30 mg/day, >30 mg/day) was included in the model.

Source: t_ef_sum_IT

TCZ QW and TCZ Q2W superior to PBO + 52 week steroid taper

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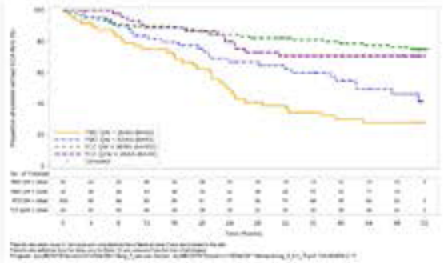
Other Secondary EPs

Figure 3 Time to First GCA Disease Flare Following Clinical Remission (ITT Population)



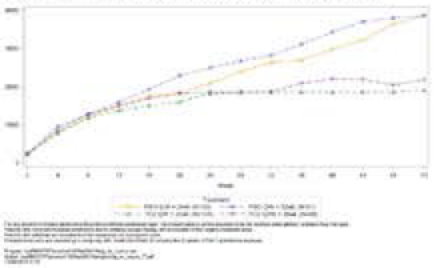
Median time to flare following remission:

PBO+26 wk group	165 days
PBO+52 wk group	295 days
TCZ QW+26 wk group	*
TCZ Q2W+26 wk group	**

* 23% and **26.5% experienced flare

Statistically lower risk of flare in TCZ QW

Figure 4 Median Cumulative Glucocorticoid Dose (mg) Over Time



Median cumulative prednisone (mg):

PBO+26 wk group	3296.0
PBO+52 wk group	3818.0
TCZ QW+26 wk group	1862.0
TCZ Q2W+26 wk group	1862.0

Includes escape therapy

In subset receiving escape, the QW group required less prednisone (3130 vs. 3847 mg)

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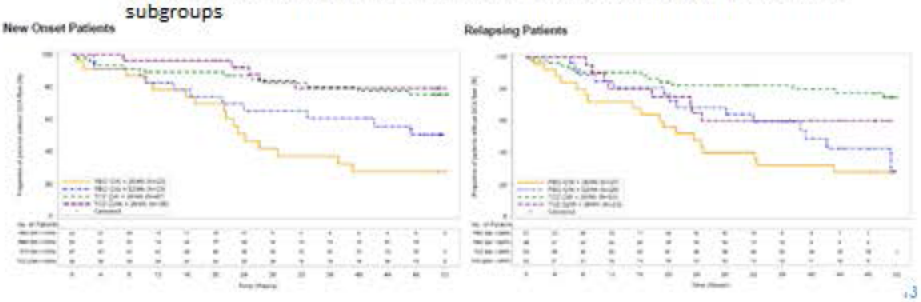
Subgroup Analyses – Disease Onset

- New onset (47%), relapsing (53%)
  - Numerically higher proportion achieving sustained remission at Wk 52 in new onset
  - In new onset, the Kaplan-Meier plot of time to first GCA flare shows overlap between TCZ QW and TCZ Q2W
  - In relapsing patients, the Kaplan-Meier plot of time to first GCA flare shows overlap between TCZ Q2W and PBO + 52. Longest time to flare in TCZ QW
  - Mean actual cumulative prednisone dose to Wk 52 lowest in TCZ QW group in both subgroups



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Safety

Overview of Adverse Events				
	PBO + 26 N=50	PBO + 52 N=51	TCZ QW + 26 N=100	TCZ Q2W + 26 N=49
# of pts with ≥1 AE, n(%)	48 (96.0)	47 (92.2)	98 (98.0)	47 (95.9)
Total number of events	470	486	810	432
Deaths	0	0	0	0
Withdrawal from study due to AE, n(%)	2 (4.0)	0	6 (6.0)	3 (6.1)
Withdrawal from treatment due to AE, n(%)	6 (12.0)	0	11 (11.0)	6 (12.2)
# of pts with ≥1 SAE, n(%)	11 (22.0)	13 (25.5)	15 (15.0)	7 (14.3)
AESI:				
Infections and Infestations	38 (76.0)	33 (64.7)	75 (75.0)	36 (73.5)
Serious Infections	2 (4.0)	6 (11.8)	7 (7.0)	2 (4.1)
Opportunistic Infections	0	2 (3.9)	0	1 (2.0)
Malignancy	1 (2.0)	1 (2.0)	1 (1.0)	0
Anaphylaxis (Sampson)	0	0	0	1 (2.0)
Serious Stroke	0	1 (2.0)	0	1 (2.0)

No serious MI, serious hepatic AEs, serious GI perforation, serious bleeding, serious demyelinating AEs

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Review of Labeling

Review of Labeling (2)

Filing and Planning

- Clinical Filing Checklist:
  - Completed, no omissions
- Advisory Committee:
  - Not recommended
- OSI Audit:
  - Not recommended
- Pediatric Development Plan:
  - Agreed iPSP is included in the sBLA

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Conclusions and Mid-cycle Deliverables

- Application is fileable, as a priority sBLA
- Mid-cycle deliverables:
  - Complete review:
    - Efficacy endpoints proposed for labeling
    - Safety in GCA population

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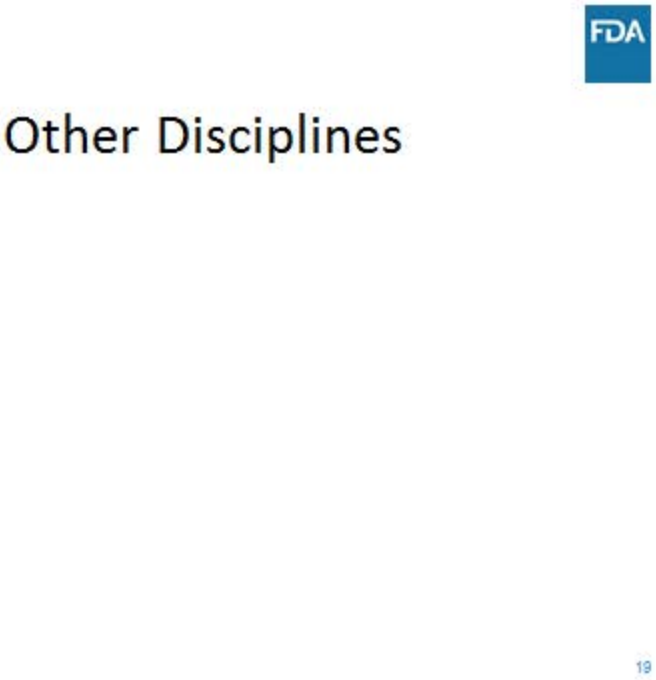
FDA
Other Disciplines
19

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL GLASER
01/05/2017

NIKOLAY P NIKOLOV
01/05/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s112

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA or Supplement

BLA Number: 125472/S-024 and 125276/S-112 **Applicant: Genentech Inc.** **Stamp Date: 11-22-16/ 11-23-16**

Drug Name: Actemra (tocilizumab) SC **NDA Type: sBLA**

On **initial** overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?		X	No new nonclinical studies were conducted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?		X	
3	Is the pharmacology/toxicology section legible so that substantive review can begin?		X	
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. No nonclinical studies were required or submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. See Comment in #1.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable. See Comment in #1.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. See Comment in #1.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable. No studies were requested.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?			Not applicable. The product label was recently updated with changes to Sections 8.1 and 8.2 (compliance with the PLLR), 12, and 13.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)			Not applicable.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____
There are no nonclinical issues in these efficacy supplements; therefore, no PharmTox review will be conducted.

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.
None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRETT R JONES
01/05/2017
No further PharmTox review will be conducted.

TIMOTHY W ROBISON
01/05/2017
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s112

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #/Supplement #:	BLA 125472/S024 BLA125276/S112
Drug Name:	Actemra® (tocilizumab)
Indication(s):	Giant Cell Arteritis
Applicant:	Roche/Genentech
Date(s):	Received: Nov 22nd and 23rd 2016
	PDUFA Due Date: May 22nd 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	William Koh, Ph.D.
Concurring Reviewers:	Gregory Levin, Ph.D., Team Leader/Associate Director
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1 EXECUTIVE SUMMARY

This review evaluated a supplemental biologics license application by Genentech for Actemra (tocilizumab or TCZ) as a subcutaneous injection for the treatment of adult patients with giant cell arteritis (GCA). The proposed indication by the applicant is 162 mg every week (QW) for treatment of adult patients with GCA. The applicant conducted a single Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-arm, 52-week study, WA28119, to provide evidence on the efficacy and safety of TCZ among adult patients with either new onset GCA or refractory active GCA disease. Study WA28119 consisted of four arms: TCZ 162 mg QW with 26-week prednisone taper, TCZ 162 mg every other week (Q2W) with 26-week prednisone taper, placebo with 26-week prednisone taper, and placebo with 52-week prednisone taper.

The primary endpoint of sustained remission at Week 52 was defined by (1) absence of signs and symptoms of GCA from Week 12 through Week 52, (2) normalization of erythrocyte sedimentation rate (ESR) (to < 30mm/hr by Week 12 without an elevation to ≥ 30mm/hr attributable to GCA after Week 12), and (3) normalization of C-reactive protein (CRP) (to < 1mg/dL by Week 12, with absence of two consecutive elevations to ≥ 1mg/dL after Week 12), along with (4) successful adherence to the prednisone taper defined by not more than 100mg of excess prednisone from Week 12 through Week 52. The primary objective compared TCZ QW and TCZ Q2W to the placebo arm with 26-week prednisone taper, and showed statistically significantly higher probabilities of sustained remission, with absolute increases versus placebo with 26-week taper of 42% (99.5% confidence interval or CI: 18% - 66%; $p<0.0001$) and 39% (99.5% CI: 12% - 66%; $p<0.0001$) respectively. The key secondary objective was to compare TCZ, to what the review team considers to be a reasonable representation of standard of care, placebo with 52-week prednisone taper; TCZ QW and TCZ Q2W both demonstrated higher probabilities of sustained remission, with absolute increases versus placebo with 52-week taper of 38% (99.5% CI: 14% - 62%; $p<0.0001$) and 35% (99.5% CI: 9% - 62%; $p=0.0002$), respectively.

Sensitivity analyses were conducted to evaluate the treatment effect on the individual components of sustained remission (1 – 4). Findings remained consistent for individual components 2 and 3 for both doses, as compared to both placebo arms. Evidence for TCZ QW based on component 1, absence of signs and symptoms of GCA, remained compelling and robust against both placebo arms. Results based on this component comparing TCZ Q2W to both placebo arms were less compelling, and there was a suggestion of greater improvement for this endpoint on QW than Q2W dosing.

Other secondary endpoints appeared consistent with the primary and key secondary objectives. Numerical trends of improvement were observed in key patient-reported outcomes, SF-36 mental component, SF-36 physical component, and patient global VAS assessment, for the dosing regimens of TCZ (either QW or Q2W) relative to both placebo with 26-week prednisone taper and placebo with 52-week taper at Week 52. There were also numerical trends suggesting that the overall prednisone dose for the TCZ QW and Q2W doses was substantially lower than both of the placebo arms. Patients on TCZ Q2W averaged slightly higher overall prednisone dose use than patients on TCZ QW.

Subgroup analyses, based on sustained remission at week 52 by age groups, gender, race, weight groups, geographic regions, or relapsing GCA status, showed numerical trends consistent with the primary findings. Interpretations within the subgroups were limited due to the much smaller number of subjects as well as the multiplicity introduced.

In summary, there was convincing evidence among patients with GCA from this single pivotal study that TCZ QW when used in conjunction with an appropriate prednisone taper is efficacious based on not only the protocol-defined sustained remission composite endpoint from Week 12 through Week 52, but also based on the absence of signs and symptoms of GCA from Week 12 through Week 52. In addition, analyses based on signs and symptoms alone suggested a higher response probability on the QW than the Q2W dosing. Evidence from TCZ Q2W for the key supportive signs and symptoms endpoint was less convincing, and supportive results of total prednisone use indicate that additional prednisone (e.g., a slower tapering schedule) may be warranted for this dosing regimen. An additional post-marketing trial would be helpful to evaluate the utility of longer term use of tocilizumab (e.g., past one year) in GCA and the appropriate dosing strategy to inform clinical practice.

2 INTRODUCTION

2.1 Overview

Giant cell arteritis (GCA) is a large and medium vessel systemic vasculitis involving inflammation of the blood vessels, typically affecting arteries around the temples, but is not limited to the vessels of the scalp and head. Because this disease typically involves swelling and thickening of the small artery under the skin called the temporal artery, another common name for GCA is temporal arteritis.

GCA may co-occur with polymyalgia rheumatica (PMR). Polymyalgia rheumatica is a condition that involves pain and stiffness in the hip and shoulder girdle associated with elevated inflammatory markers. Patients may present with both diseases together or with only one. Approximately half of the GCA patients may present with symptoms of PMR. Conversely, approximately 20% of the PMR patients have symptoms of GCA (Salvarani et al 2012).

GCA typically occurs in older adults over the age of 50. The most common symptoms of this disease are cranial symptoms including headache, scalp tenderness, jaw claudication. However, headache due to GCA can occur anywhere around the skull. Other signs and symptoms include scalp tenderness and jaw claudication. The complications of this disease can involve permanent vision loss, stroke, and aortic aneurysm.

The gold standard for the diagnosis of GCA is biopsy. Recently, there are new emerging trends of the use of imaging, such as ultrasound, magnetic resonance imaging, etc, to diagnose the disease. It is common that biopsy of the temporal artery is used to diagnose this disease.

Currently, the standard of care for patients diagnosed with this disease is a high dose of daily oral corticosteroids upon suspicion of the diagnosis of GCA, or even prior to biopsy of the temporal artery, or other evaluations to confirm the diagnosis. Once the disease is controlled based on resolution of symptoms and normalization of inflammatory markers, a slow corticosteroid taper

can be initiated such that most patients are treated with a prolonged steroid taper over a year or longer.

2.1.1 Class and Indication

Actemra® (tocilizumab) is a humanized monoclonal antibody directed against the IL-6 receptor and has been approved by FDA for treatment of rheumatoid arthritis via intravenous (IV) and subcutaneous administration, polyarticular juvenile idiopathic arthritis (JIA) via IV administration, and systemic JIA via IV administration. Tocilizumab binds to the membrane and soluble forms of IL-6R and prevents the binding of cytokine IL6 (includes soluble IL6) from binding to the receptor. A known and direct implication of use of tocilizumab is a direct decrease in C-reactive protein (CRP) levels.

The applicant has proposed that tocilizumab be indicated for treatment of adult patients with giant cell arteritis with a proposed dose of 162 mg every week subcutaneously. The applicant has submitted the results of a single pivotal Phase 3 study (WA28119) to support the safety and effectiveness of the proposed dosing of 162 mg tocilizumab, administered subcutaneously once every week, in combination with a tapering course of glucocorticoids, for treatment of adult patients with giant cell arteritis. The applicant also proposed that tocilizumab could be used alone after discontinuation of glucocorticoids. This BLA supplement is given a Priority Review Designation.

2.1.2 History of Drug Development

The applicant has had multiple meetings with the Agency during the course of clinical development. Below is a summary of the key interactions of importance for this statistical review. Selection of appropriate control group, steroid tapering regimen, blinding to values of inflammatory markers, and the definition of the primary endpoint were points of discussion.

The applicant submitted a request for a pre-IND meeting outlining the proposed clinical development plans for tocilizumab as a proposed treatment in adult patients with GCA. The Agency responded with the following general concerns: (1) The proposed doses and subcutaneous administration in the Phase 3 trial were supported by information using another route of administration; (2) The placebo arm with 26-week steroid taper was not the current standard of care for treatment of GCA; and (3) The Agency was also concerned that investigators may become unblinded to the treatment arm should they be aware or have access to results of inflammatory markers, especially when a placebo control group is used, since tocilizumab is expected to directly inhibit the production of acute phase reactants.

Specifically, the applicant asked if the successful completion of the one pivotal phase 3 trial would be sufficient to support the GCA indication. The Agency stated that because of the limited information available, and the concerns described, it was not possible to conclude that a successful study as proposed would be sufficient to support a new indication in GCA. The Agency however stated that, in principle, in accordance with the Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, "it is

possible that a single study might be sufficient to support the new indication, if it is a multicenter trial, with robust treatment effect size, and consistency of effect among efficacy endpoints and subpopulations. This would also depend on a lack of new safety signals in the new population that would require further characterization."

During the PIND face-to-face meeting, the Agency re-iterated the above concerns and recommended incorporating a control arm with a longer steroid taper consistent with standard-of-care. The Agency suggested that the applicant consider the infliximab GCA study (Hoffman et al. 2007) to help design a more appropriate tapering strategy for its product. The applicant included a placebo arm with 52-week prednisone taper following this meeting.

A Special Protocol Assessment (SPA) was submitted by the applicant with the study control still based on a 26-week prednisone taper with the primary endpoint evaluated at Week 52. The Agency disagreed and reiterated concerns on the proposed choice of study control based on a 26-week prednisone taper. The Agency was also concerned that patients in the placebo arm would be more likely to have a flare since they would only be treated with 26 weeks of steroids while the primary assessment is at Week 52. The Agency agreed that the proposed dual assessor approach appeared reasonable to "mitigate the risk of unblinding investigators to the study treatment."

The applicant submitted the Statistical Analysis Plan (SAP) for Study WA28119 to request feedback from the Agency. The Agency expressed various concerns related to the primary endpoint, non-inferiority comparison with placebo arm with 52-week prednisone taper (standard of care), and definition of flare. Specifically, the primary analysis compared patients on tocilizumab at Week 52 with the placebo arm with only a 26-week taper and would not be a fair comparison since the placebo arm is an undertreated population relative to standard of care. Even though the applicant included the placebo arm with 52-week prednisone taper as recommended after the PIND meeting, the Agency did not agree with the applicant's proposal for the non-inferiority comparison with the placebo arm with 52-week prednisone taper. The Agency expressed further concerns that the proposed non-inferiority margin for the comparison against the placebo arm with 52-week prednisone taper was not adequately justified. Lastly, the definition of flare includes effects of inflammatory markers and thus can bias the results in favor of TCZ since TCZ has a direct effect on lowering the production of acute phase reactants. Other statistical comments noted that subgroup analyses by age, race, gender, and region were not prospectively planned.

A revised version of the SAP was later submitted to the Agency. The Agency reminded the applicant that subgroup analyses by age, race, gender, and region should be prospectively planned. Furthermore, the Agency commented that the applicant should include any secondary endpoints that may be proposed for inclusion in the labeling in the prespecified statistical analysis hierarchy. In this revised version of the SAP, the Agency recommended that supportive analyses be prospectively planned to determine the contribution of the treatment effect on each of the (individual) components of the primary endpoint, sustained remission from Week 12 through Week 52. Such supportive analyses are important to understand whether the treatment effect may be driven by effects of inflammatory markers, adherence, or steroid tapering, rather than by effects on the signs and symptoms of the disease. The Agency also questioned the utility of the non-inferiority (NI) comparison between tocilizumab with 26-week prednisone taper and

placebo with 52-week prednisone taper. Unlike NI studies where a placebo control arm is absent, study WA28119 has a placebo plus standard of care control arm and thus should directly evaluate the superiority of tocilizumab with 26-week prednisone taper over placebo with 52-week prednisone taper. The choice and justification of the margin selection based on preservation of only 50% of the treatment effect against a slower steroid taper was also considered inadequate.

A pre-BLA face-to-face meeting was initiated by the applicant to discuss the planned submission. In a written response to the applicant, the Agency reiterated that the application should include supportive analyses to understand the contribution of the components of the primary endpoint to address GCA remission. Additional similar analyses based on patient global score and SF-36 scores at week 52 should also be included. The Agency was also interested in the intent-to-treat estimand, i.e., the comparisons should include all observed data regardless of adherence to treatment, levels of acute phase reactants, and adherence to steroid tapering regimen. The Agency also requested direct comparisons (such as estimated differences, confidence intervals) between doses of tocilizumab with respect to key efficacy and safety outcomes.

The applicant presented the key findings from WA28119 during the meeting and sought clarification from the Agency on the additional analyses required and whether an analysis of time to first flare following clinical remission was sufficient. The Agency requested that symptomatic flare be defined based on symptoms only, and should not include CRP, ESR, or steroid tapering adherence as components. The Agency also requested additional supportive analyses of secondary endpoints based on patient-reported outcomes at key time points including all observed data. The applicant agreed with the Agency's request to evaluate the potential impact of missing data.

2.1.3 Specific Studies Reviewed

The applicant conducted one pivotal study, WA28119, to determine whether tocilizumab is efficacious and safe as compared to placebo among patients with GCA. The objective of this statistical review is to determine whether tocilizumab, relative to standard of care, i.e., the placebo plus 52-week steroid taper arm, is efficacious in treating the signs and symptoms of patients with GCA. The applicant investigated two dosing regimens each with a 26-week prednisone taper in this pivotal study, tocilizumab 162mg every week subcutaneously and tocilizumab 162mg every two weeks subcutaneously. The applicant included two placebo arms, a placebo arm with a 26-week prednisone taper and a placebo arm with a 52-week prednisone taper.

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed under the network path \\cdsesub1\evsprod\BLA125472\0116.

Additional information request (IR) responses related to evaluating the efficacy of TCZ are summarized in Table 1.

Table 1 Data links, dates, and summary of information requests made to applicant.

Information request links	Date of response	Summary
\\cdsesub1\evsprod\BLA125472\0120	Dec 23 2016	Demographic subgroup analyses, statistical methods for subgroups, text files of source code, all protocol amendments, and all revisions of the statistical analysis plan.
\\cdsesub1\evsprod\BLA125472\0123	Jan 30 2017	The Data Monitoring Committee charter, meeting agenda (both closed and open), meeting minutes of both open and closed sessions, source code for statistical analysis and dataset construction, clarification of disposition summary tables and figures, and all protocol revisions were provided
\\cdsesub1\evsprod\BLA125472\0128	Feb 15 2017	Disposition flags, disposition definitions, adverse events, documentation of back-calculating missing prednisone starting dose at baseline.
\\cdsesub1\evsprod\BLA125472\0130	Feb 15 2017	Revision to the response submitted under the link \\cdsesub1\evsprod\BLA125472\0128.
\\cdsesub1\evsprod\BLA125472\0138	Apr 06 2017	Response to clarification of data for subjects that were handled differently for Week 52 patient-reported outcomes. Clarification on assumptions on how exposure to prednisone dose was calculated.
\\cdsesub1\evsprod\BLA125472\0140	Apr 13 2017	Further clarification on laboratory measurements at Week 52, AEs, patient-reported outcomes not listed in Apr 06 2017, and other datasets originally submitted for this review.

[Source: Reviewer.]
Abbreviations: AEs=adverse events.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Datasets were submitted in legacy format. Additional steps were required to derive specific variables, such as cumulative prednisone dose and signs or symptoms of GCA, from the submitted datasets. In general, the quality of data submitted for efficacy analyses was adequate. However, specific details were lacking in the applicant's define files to replicate some important analyses. This was clarified upon information request from FDA.

During the review process, I noted that some patients' week 52 data were handled differently and were not incorporated in the original datasets for some analyses. This was further clarified by the applicant, dated Apr 6 2017 and Apr 13 2017, and appropriately revised datasets and analyses were re-submitted upon information request from FDA. More details are described in 3.2.2.

3.2 Evaluation of Efficacy

3.2.1 Study Design WA28119

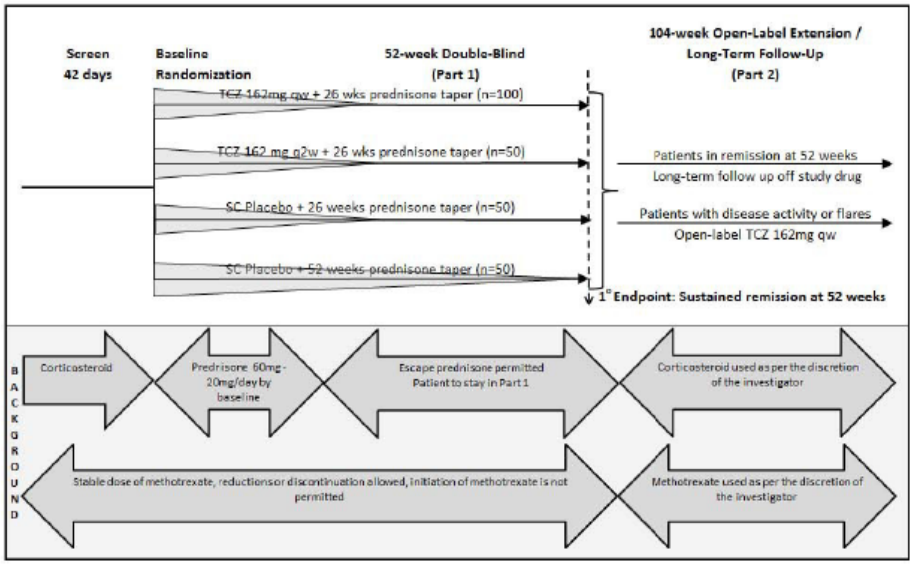
Study WA28119 was a randomized, double-blind, multi-site, multiple arm, parallel-group, placebo-controlled study conducted to assess the efficacy and safety of tocilizumab (TCZ) among adult patients with GCA.

The study design consisted of two distinct periods: a 52-week double-blind period after randomization and a further 104-week open-label extension following the end of the 52-week double-blind period (as shown in Figure 1). The study consisted of the following treatment arms: placebo with 26-week prednisone taper, placebo with 52-week prednisone taper, TCZ every 2 weeks (Q2W) with 26-week prednisone taper, and TCZ every week (QW) with 26-week prednisone taper. Randomization was stratified by baseline use of prednisone dose dichotomized as either ≤ 30 mg/day or > 30mg/day. The extension period enrolled only subjects who completed the 52-week study. The open-label extension or long-term follow-up period was uncontrolled and was not included in the efficacy review.

The study was designed to control the overall type I error probability at the two-sided 1% level. No interim analysis was planned. An independent Data Monitoring Committee (iDMC) was convened to regularly review safety data at least twice a year.

The primary objective of study WA28119 was to determine whether TCZ compared to placebo, in combination with 26-week prednisone taper, was efficacious as a treatment for adult patients with GCA. The key secondary objective in the protocol was to determine whether the doses of TCZ with 26-week prednisone taper regimen were non-inferior as compared to placebo with 52-week prednisone taper regimen.

Figure 1 Study design for WA28119



[Source: Module 5.3.5.1, clinical study report under core report Figure 1.]

The protocol-defined primary endpoint was sustained remission from Week 12 through Week 52. This primary endpoint was a complex composite endpoint. To meet the definition of

sustained remission, a patient must (1) have attained GCA remission by Week 12 (induction of remission), and (2) have sustained GCA remission at all study visits between Week 12 through Week 52 (sustained remission), and (3) have adhered to the protocol-defined prednisone taper regimen (the total amount of excess prednisone used from Week 12 through Week 52 must be less than 100mg corticosteroids relative to the pre-planned patient-specific tapering regimen).

GCA remission was defined by (a) the absence of a flare assessed by the investigator and (b) normalization of CRP (< 1mg/dL). A flare, as determined by the investigator (Protocol version 4 onwards), was defined as the *recurrence* of signs and symptoms of GCA and/or an ESR ≥ 30mm/h attributable to GCA. Non-normalization of CRP was defined by elevated CRP level (≥ 1mg/dL) on two consecutive visits or an elevated CRP level at a visit combined with a missing value at the next consecutive visit.

The protocol-defined prednisone taper was based on a monotone non-increasing regimen. The patient and the investigator was unblinded to the amount of prednisone dose at the beginning of the study until the dose dropped below 20mg/day.

Randomized patients were assessed weekly for signs and symptoms of the disease for the first four weeks of the study, and then every 4 weeks from Week 4 to Week 52. More specifically, evaluation of signs and symptoms of GCA included:

- Fever (≥ 38°C or 100.4°F),
- Symptoms of PMR (morning stiffness and/or pain, in the shoulder and/or hip girdles),
- Localized headache, temporal artery or scalp tenderness,
- Visual signs or symptoms such as acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy (A-AION), transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes) ,
- Jaw or mouth pain,
- New or worsened extremity claudication,
- Other features judged by the Clinical Assessor to be consistent with a GCA or PMR flare.

Blinding: TCZ is known to suppress levels of acute phase reactants. Knowledge of acute phase reactant levels could unblind patient treatment assignment, potentially inducing biases in the assessment of the primary endpoint of sustained remission. The applicant used a dual assessor approach to maintain this blind.

An Efficacy Assessor was a rheumatologist responsible for the assessment of the clinical signs and symptoms of GCA (without access to CRP and ESR levels), the assessment of adherence to the protocol-defined prednisone taper regimen, and the recording of adverse events during the 52-week double-blind period (Part 1). An independent Safety Assessor, who could not be the same as the Efficacy Assessor, had access to only the patient's laboratory data.

The protocol stated that it was "mandatory and essential that assessments by the Efficacy Assessor be completed before assessments by Safety Assessor." Furthermore, the Safety Assessor would only communicate the ESR findings to the Clinical Assessor if the patient's ESR was above 40mm/hr. If the ESR fell outside the ULN (as determined by the clinical laboratory assay standards) and was strictly less than 40mm/hr, the Safety Assessor was to repeat the ESR test and *only* notify the Efficacy Assessor if the repeated ESR test measurement is ≥ 30mm/hr. The ULN was not stated in the protocol.

Use of escape prednisone: Additional prednisone use was permitted by patients during the study under the following conditions: Patients who were evaluated by the clinician to have a disease flare of GCA, either based on knowledge of elevated ESR ≥ 30mm/hr or by an investigator determination of a flare based on signs or symptoms of GCA, were allowed to increase the amount of steroid use during the study. Patients who were unable to adhere to the steroid taper were considered to have escaped.

Patients were permitted use of short-term corticosteroids during the study, if deemed necessary for the management of the patient, for the management of events such as a serious infection or if needed to prevent adrenal insufficiency. Short-term use was not considered to qualify as escape unless the total amount of such steroid use between weeks 12 through 52 was greater than 100mg. Corticosteroids via intra-articular, intravenous or intramuscular routes of corticosteroids were not permitted.

Patient were also instructed to keep diary records of pills taken for the steroid used in order to allow assessment of adherence to the prednisone pre-planned taper. Oral calcium and vitamin supplementations were mandatory for prevention of glucocorticoid-induced osteopenia/osteoporosis in the absence of contraindications to their use.

Other secondary objectives: Other secondary objectives of the study included determining whether doses of TCZ in combination with 26-week prednisone taper regimen were efficacious over the placebo groups based on the following endpoints: (A) time to GCA disease flare after clinical remission, (B) cumulative prednisone dose over 52 weeks, (C) patient global assessment of disease activity on a visual analogue scale (VAS) of 0 – 100mm at week 52, and (D) change from baseline in SF-36 health survey scores at Week 52.

Exploratory secondary objectives: The applicant also specified several exploratory secondary objectives such as the evaluation of (1) maintenance of remission by comparing the proportion of patients who remain in sustained remission at 64 weeks (and every 12 weeks thereafter), (2) efficacy of TCZ based on annualized relapse rate, (3) remission rates over time, (4) Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) score, (5) EuroQol 5D (EQ-5D) version 5L score, and (6) duration of corticosteroid use by treatment group.

A summary of the protocol revision history is provided in Table 2 based on the applicant-submitted materials.

The applicant clarified that Protocol Version 3 was current in all regions at the time of the study. In the final Version 5 of the Protocol, Section 6 states that all statistical analyses will be specified in the SAP which will be finalized prior to locking and unblinding of the study database.

The study database is stated to be locked for primary analysis when the last patient has completed his or her Week 52 assessment or has been withdrawn.

3.2.2 Statistical Methodologies

The SAP was first issued on Jan 02 2015 and the final version 2 of the SAP was issued on Apr 15 2016. However, there were minor revisions between Version 1 and 2 of the SAP. According to the summary of clinical efficacy (Module 2.7), the clinical cut-off (also referred to as data cut-

off) date for the 52-week analysis was Apr 11 2016. Thus, it is unclear whether the minor revision in version 2 of the SAP occurred prior to data unblinding. All statistical methodologies provided are based on version 2 of the applicant's SAP. In the CSR, there were additional modifications to the planned statistical analyses not described in version 2 of the SAP. I regarded these post-hoc changes to the statistical analyses as exploratory in nature.

Table 2 Revision histories for the protocol.

Protocol Version	Global Protocol	Canada-specific
Version 1	July 20 2012	
Version 2	Oct 19 2012	
Version 3	Feb 08 2013	
Version 4 (Canada)		Jun 07 2013[a]
Version 4	Jan 22 2014[b]	
Version 5 (Canada)		Jan 22 2014[b]

[Source: Applicant's response to Question 6 on Jan 30 2017. Reviewer added the footnotes.]
[a] : Canada-specific protocol has additional text to clarify the standard of care for corticosteroid treatment of patients with new-onset giant cell arteritis during the screening period. Global protocol remained as Version 3.
[b] : Definition of flare has been modified from "Flare is defined as the recurrence of signs or symptoms attributable to GCA" to "Flare is *determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or ESR ≥ 30 mm/hr attributable to GCA"* from Version 5 onwards.

3.2.2.1 Applicant's Statistical Methodologies

The primary analysis population consisted of all randomized subjects who received at least one dose of study medication or the *Intent-to-Treat (ITT)* population. The ITT population was also used for statistical analysis of other secondary and exploratory secondary endpoints.

3.2.2.1.1 Statistical significance/Multiplicity adjustment

Study WA28119 was designed to control the overall type I error probability at the two-sided 1% level. A multiplicity adjustment was made for the two TCZ doses by evaluating each dose at the two-sided alpha level of 0.005 with hierarchal tests of the primary and key secondary objectives.

Hierarchy 1 evaluated the superiority of TCZ QW with 26-week prednisone taper vs placebo with 26-week prednisone taper, followed by the non-inferiority of TCZ QW with 26-week prednisone taper compared to placebo with 52-week prednisone taper.

Hierarchy 2 evaluated the superiority of TCZ Q2W with 26-week prednisone taper vs placebo with 26-week prednisone taper, followed by the non-inferiority of TCZ Q2W with 26-week prednisone taper compared to placebo with 52-week prednisone taper.

For the key secondary objective, a 99.5% CI was used to assess the non-inferiority comparison between TCZ with 26-week prednisone taper compared to placebo with 52-week prednisone taper. The applicant prespecified that a lower bound based on the two-sided 99.5% CI exceeding -22.5% would "demonstrate non inferiority" as compared to placebo with 52-week prednisone taper, "allowing for preservation of at least 50% of a minimum treatment effect of prespecified treatment effect of 45% observed with corticosteroid therapy alone."

3.2.2.1.2 Protocol-defined primary efficacy endpoint and statistical analyses

Treatment arms were compared using the difference in the probability of patients remaining in sustained remission at Week 52 relative to the placebo group. Crude unadjusted estimates of the probability were calculated using the sample proportions. P-values were obtained based on the Cochran-Mantel-Haenszel method based on normal approximation adjusting for baseline categories of prednisone starting level. Unadjusted confidence intervals for the difference in proportions were based on normal approximation and presented at the 99.5% level.

Non-responder imputation was used for the primary endpoint under the following situations. Patients who flared/escaped, withdrew from the study prior to Week 52, or for whom remission status could not be determined were classified as non-responders. Patients who did not achieve remission within 12 weeks of baseline were also classified as non-responders. Patients who had elevated CRP at a scheduled visit and were missing CRP values at the next consecutive visit were defined to be non-responders.[1] A subject with an elevated CRP at, for example, visit Week 52, was automatically considered a non-responder since the future CRP level was missing. If a patient's "remission status could not be determined" at Week 52 due to early withdrawal, they will be classified as non-responders for the primary endpoint of sustained remission from Week 12 through Week 52. The applicant implemented this based on the patients' remission status at Week 52 to obtain the primary endpoint.

No documentation was provided on how missing data for other components (signs or symptoms of GCA, or flare) were handled. The protocol did not include scenarios where intermittent missingness of CRP measurements happened prior to an elevated CRP at the next visit.

3.2.2.1.3 Planned sensitivity analyses for the primary efficacy endpoint

The applicant also proposed several sensitivity analyses in the SAP to assess the robustness of their primary endpoint results to violations in missing data assumptions as well as to address the Agency's concern about effects on the primary composite endpoint being potentially driven by effects on inflammatory markers.

A tipping point analysis, referencing the approach of Yan et al. 2009, was used to evaluate the robustness of the primary endpoint results in the presence of missing data. In the applicant's tipping point analyses, patients who discontinued from the study but had a GCA flare or escaped prior to withdrawal were considered non-responders; the responder status of patients who discontinued from the study but had not had a GCA flare prior to withdrawal or had not escaped was imputed by exploring all possible combinations of numbers of responders among the missing patients with unknown responder status on the different treatment arms.

The applicant also included a sensitivity analysis based on signs and symptoms of the disease by excluding the requirement for absence of elevated CRP in the definition of remission to evaluate the possibility that the known effect of TCZ on acute phase reactants could be driving the

[1] This statement was added in SAP version 2 dated Apr 15 2017 after Week 52 data for the last remaining patient was collected on Apr 11 2017.

primary endpoint results. It is noted that the applicant only excluded CRP from the definition of sustatined remission; ESR was not excluded.

A planned sensitivity analysis based on sustained remission from Week 12 through Week 52 regardless of adherence to steroid taper was also included by the applicant under the exploratory analyses section of the SAP. This analysis used a similar non-responder imputation approach as the primary analysis.

3.2.2.1.4 Statistical analysis procedures for "Other secondary endpoints"

Statistical analyses procedures were prespecified for "*Other secondary endpoints"* (A-D as denoted in 3.2.1). Analyses included all randomized patients who received at least one TCZ or placebo injection. The treatment effect of interest was based on the difference in the change from baseline at Week 52 for the TCZ arm of interest relative to the placebo arm with 26-week prednisone taper. Similar comparisons of TCZ arms were made relative to the placebo arm with 52-week prednisone taper.

The following statistical analysis methods and *handling of missing data (in italics)* were used for the other secondary endpoints:

For the time to first flare following GCA remission, a Cox proportional hazards model was fit to the time interval from when the patient entered GCA remission to the time of the first protocol-defined flare, adjusting for treatment group and categorical baseline prednisone level. *Patients who withdrew or discontinued study completely prior to Week 52 were censored.*

Cumulative prednisone dose was analyzed using a van Elteren test adjusting for starting prednisone dose. Median total prednisone dose over the 52 weeks for each treatment group and the corresponding 95% CI for the median was presented. *If the patient had discontinued from the study completely prior to Week 52, the cumulative dose from the patient's last visit was used as the final measurement in the statistical analysis. No imputation strategy was proposed by the applicant. Missing records of the patient's use of prednisone were imputed based on the minimum dose tablet provided to the patient from the pack.*

For the patient-reported outcomes (PROs), namely, the patient global assessment, physical component of SF 36, and mental component of SF-36, a linear mixed effects, repeated measures model adjusting for treatment group, binary baseline prednisone dose (≤ 30mg/day, > 30mg/day), categorical visit week (weeks 12, 24, 36, 48, 52), treatment group by visit interaction, baseline prednisone dose by visit interaction, continuous baseline measurement, and interaction of continuous baseline measurement with visit was fit to the change from baseline measurement at each visit. Within-subject variation across visits was presumed to follow an unstructured variance-covariance structure, and the Kenward-Roger approximation was used to estimate the degrees of freedom for pairwise comparisons. *Section 4.10.1 of the SAP stated that post-escape observed data for SF-36 was to be set to missing. If patient withdrew from the study prior to Week 52, no imputation was performed. There were no missing data rules or post-escape data handling rules for patient global VAS assessment.*

3.2.2.1.5 Statistical analysis approach for "Exploratory secondary endpoints"

SAP version 2 stated that these endpoints are "exploratory; therefore, no adjustment for multiplicity will be made (i.e., statistical tests, where applicable, will be performed with a significance level of 1%), and no claim of statistical significance will be made." In addition, descriptive statistics such as means and standard deviations, or counts and percentages, were reported for these exploratory secondary endpoints in the applicant's CSR. In this review, results for these endpoints were not evaluated or reported.

3.2.2.1.6 Methodologies utilized in the CSR but not planned in SAP

The applicant included results from additional statistical procedures in the CSR that were not planned in version 2 of the SAP. I regarded these analyses to be post-hoc since they were not pre-specified in the SAP or protocol. The following is a list of statistical analyses relevant to this review.

- Superiority of the key secondary objective comparing TCZ to the placebo with 52-week taper arm was to be tested if non-inferiority was met. The alpha level was claimed to not require further adjustment because this was explained by the applicant to be a closed testing procedure.
- The choice of pooled vs unpooled standard deviation used in computing the 99.5% CI for the primary endpoint was noted to be different for the evaluation of the primary and secondary objectives.
- Reported results for patient global VAS assessment at Week 52 were based on data collected prior to escape with observed data after escape set to missing.[2] A separate sensitivity analysis included all observed data regardless of escape.
- Statistical procedures for subgroup analyses by demographic subgroups were not described. These procedures were later clarified in an IR response dated Dec 23 2016.

3.2.2.1.7 Other Issues

In the original submission, the number of subjects with available Week 52 data for patient-reported outcomes, namely SF-36 and patient global VAS assessment, were noticeably smaller than the number of patients who completed Week 52 of the study. In the IR response dated Apr 06 2017, the applicant clarified that the data were handled slightly differently for these subjects and re-submitted the requested PRO outcome data for SF-36 and patient global VAS assessment. Similar observations were noted for the laboratory results.

Subsequent clarifications were made with the applicant on whether other datasets submitted for review had similar issues. The applicant clarified, on Apr 13 2017, and re-submitted the laboratory measurements, EQ-5D, and FACIT-Fatigue data that included these observations that

[2] Refer to Table 31 of the CSR in Module 5.3.5.1.

were inadvertently omitted for review. In this review, the revised datasets for PRO outcomes, dated Apr 13 2017, will be the focus for describing the results.

3.2.2.2 Reviewer's Additional Methodologies

The applicant chose stringent Type 1 error rate control at the level of 1%, with the Type 1 error rate equally distributed across the doses. Thus, 99.5% CIs are presented for all sensitivity analyses related to the primary endpoint. I used 99% CIs for summarizing the remaining applicant results for "*Other secondary objectives"* to be consistent with the Type 1 error rate of the study design while acknowledging that multiplicity issues still exist. The time to first GCA flare following GCA remission was not included in this review because it does not reliably address a meaningful scientific question; I provide more detailed remarks on the utility of this statistical analysis in 5.1.

3.2.2.2.1 Superiority comparison with placebo arm with 52-week prednisone taper

In this application review, I conducted superiority comparisons of TCZ relative to the placebo arm with 52-week prednisone taper which more appropriately addressed the efficacy of TCZ instead of the SAP defined non-inferiority comparison. The focus on the superiority comparison is consistent with FDA correspondence to the applicant during the IND stage.

3.2.2.2.2 Supportive analyses of primary endpoint of sustained remission from Week 12 through Week 52

The sensitivity analyses proposed by the applicant based on either sustained remission regardless of normalization of CRP or sustained remission regardless of steroid taper only exclude a single component of the composite outcome; thus, treatment effects on these endpoint could still be influenced by other components of the composite endpoint (e.g., ESR level) and these analyses do not directly assess the individual components of the composite endpoint.

Therefore, I conducted additional supportive statistical analyses based solely on (1) absence of signs and symptoms of GCA from week 12 to week 52, (2) absence of elevated ESR greater than or equal to 30mm/hr attributable to GCA from week 12 to week 52, (3) absence of elevated CRP from week 12 to week 52, and (4) successful prednisone taper. The analysis based on the absence of signs and symptoms of GCA regardless of acute phase reactants, adherence to prednisone taper, and adherence to study treatment is considered critical to remove the dependence of the endpoint on levels of acute phase reactants and successful tapering and to understand whether TCZ provides direct patient benefit by improving the signs and symptoms of GCA relative to an appropriate standard of care.

Supportive descriptive analyses of the proportion of patients in sustained remission based on absence of signs and symptoms of GCA from weeks 12 through various protocol-defined visits week were used to characterize trends over the course of the study. The tipping point analysis conducted by the applicant varied the possible outcomes of patients missing data on the primary

endpoint but did not address missing data for this key supportive analysis of signs and symptoms alone. Therefore, I conducted an additional tipping point analysis analogous to the applicant, based on absence of signs and symptoms of GCA, to evaluate the robustness of this critical analysis by exploring all possible responder outcomes of patients who discontinued prior to Week 52. Descriptive analysis of the proportion of patients without signs and symptoms of GCA at any visit week was also included.

The additional missing data handling proposed in version 2 of the SAP may have been planned after data unblinding. Therefore, we re-evaluated the primary endpoint with removal of the clause stating that a patient with a missing visit following an elevated CRP would be considered a non-responder.

An additional analysis of the primary sustained remission endpoint was also conducted treating subjects who discontinued double-blind treatment as non-responders. This approach was not applied to the analyses of the individual components because the objective in these analyses was to estimate the treatment policy estimand in the real world setting by evaluating the effect of TCZ relative to placebo on patient symptoms regardless of the influence of other components, i.e., regardless of inflammatory marker levels, regardless of prednisone adherence, and regardless of adherence to study drug. Considering patients who discontinued treatment to be non-responders in the component analysis could bias results for this estimand due to potential differences in the subsets of patients who adhere to study drug across the treatment arms.

3.2.2.2.3 Statistical procedures for standard errors for primary and key secondary comparisons

The applicant did not prespecify the methodology for calculating standard errors to construct confidence intervals, and chose different statistical procedures for the primary and key secondary analyses. The lack of pre-specification is of concern because the applicant could have chosen the methodology that produced the most favorable results. I evaluated results using the different possible approaches to ensure that findings were consistent regardless of the reported methodology. I reported results based on the pooled standard errors in this review since (a) we are interested in superiority comparisons between the TCZ arms and placebo with 52-week prednisone taper; (b) the applicant chose the pooled standard error for its 99.5% confidence interval for superiority comparison relative to placebo with 26-week prednisone taper; and (c) it is useful to note that with an unequal randomization ratio (such as 1:2 randomization), the pooled standard error can sometimes be much smaller than the unpooled standard error (simulation results not shown).

3.2.2.2.4 Cumulative prednisone dose at Week 52

The applicant included concomitant use of glucocorticoids via oral, intravenous, intramuscular, intra-arterial, subcutaneous, and "other" routes of administration in the derivation of cumulative prednisone dose. These routes of administration were considered reasonable by the medical

Reviewer to reflect systemic glucocorticoid exposure.[3] Subjects who had local injections for hip tendinitis, bursitis, and carpel tunnel were included as "other" routes of glucocorticoids administration.

The analysis of cumulative prednisone taper at Week 52 was based on the last observation of the total amount of cumulative prednisone used in the study. In order to estimate the difference in total steroid use over 52 weeks between arms in all patients regardless of adherence to treatment, the analysis therefore presumes that subjects who withdrew from the study did not use any additional prednisone after dropout, which is implausible. In this review, I included descriptive statistics of the cumulative prednisone dose accounting for the duration of time the patient was in the study. This summary measure described the total prednisone dose standardized to the follow-up of the subject in the study. This analysis assumes that steroid use on study is reasonably representative of steroid use after dropout, which is a strong and unverifiable assumption but is perhaps more reasonable than the assumption that no additional steroids would be used. To compare treatment groups with respect to the total prednisone dose per year, I included a post-hoc analysis using a linear regression, allowing for heteroscedasticity, on the logarithm (base 2) of the total cumulative dose up to last follow-up adjusting for logarithm (base 2) of the total time of follow-up (Weeks), treatment group, and baseline prednisone starting dose. The inclusion of total follow-up time in the model rather than using the standardized metric is used to avoid introducing spurious correlation commonly observed in epidemiological research (Kronmal 1993). This parameter is useful if comparison of total dose between treatment groups on a ratio scale is clinically relevant.

3.2.2.2.5 Analysis of patient-reported outcomes

The applicant's analysis excluded observed data after patients moved to escape prednisone or discontinued study treatment. It is unclear what estimand the applicant was targeting. I regarded the statistical analyses for PROs based on all randomized patients regardless of escape or adherence to prednisone taper (i.e., targeting the intent-to-treat or de facto estimand) to be the relevant analyses to evaluate the effects of TCZ on these direct measures of how patients function and feel. Patients on the placebo arm who were described as having escaped were still receiving standard of care treatment, i.e., additional prednisone to treat the signs and symptoms of GCA. The analysis including all observed data preserves the integrity of the randomization and thus guarantees reliable inference based on potential differences in effects of treatment strategies when there is no missing data. The presence of missing data presents additional issues because the proposed MMRM model further relies on strong and unverifiable assumptions about the missingness mechanism, in addition to assumptions of constant variance and normality. I reported the observed means, standard deviations, and number of subjects available for PROs rather than the estimated means by treatment arm by visit from the MMRM model.

[3] Patient 10205 and 10041 were listed as receiving intramuscular steroids. Based on the indication, the Medical reviewer noted that patient 10041 was likely to have received a bursal injection. Patient 10205 had received 3 doses of steroids for "ischiatic pain left side." The Medical reviewer considered these to be reasonable routes of administration because they were considered systemic exposure to corticosteroids which might impact the results of the study (whereas eye drops would be unlikely to have any impact on GCA activity).

3.2.2.2.6 Summary of other statistical methods and software used

Descriptive tables, disposition tables, and key efficacy results were conducted in STATA 14.0. R 3.3.1 was used to conduct the tipping point analysis and cumulative prednisone analysis. SAS 9.4 was used for the repeated measures mixed model analysis. All graphics were made using R 3.3.1. Numerical comparisons between the choices of pooled standard error versus unpooled standard error were conducted in R 3.3.1. CIs for subgroups were displayed at the 95% level. P-values are two sided.

3.2.3 Demographic and Baseline Characteristics

A total of 363 patients were screened. Of these, 251 patients who met eligibility criteria were randomized into the following treatment arms in a 1:1:1:2 ratio: placebo in combination with 26-week prednisone taper (n=50), placebo in combination with 52-week prednisone taper (n=51), TCZ Q2W in combination with 26-week prednisone taper (n=50), and TCZ QW in combination with 26-week prednisone taper (n=100).

Descriptive statistics relating to the patient demographics, key anthropometric variables, disease features at diagnosis, and disease characteristics at baseline are presented in Table 3, Table 4, Table 5, and Table 6 respectively. One patient from the TCZ Q2W arm was included in the descriptive statistics but excluded from analyses of subject disposition for discontinuation of double-blind treatment, subject disposition for study discontinuation after starting treatment, and primary and secondary endpoints.[4]

3.2.3.1 Demographics

Patient demographics and anthropometric variables were generally balanced across the treatment groups as shown in Table 3. Screened patients randomized into the study were at least 50 years of age and averaged 69 years at baseline. About 70% of the subjects were aged 65 years and above; 70% of the patients were female. The majority (> 94%) of the patients were white and neither Hispanic nor Latino.

3.2.3.2 Baseline disease features

More than 95% of the patients had a history of elevated ESR > 50mm/hr (Table 4). A history of elevated CRP > 2.45mg/dL was reported in the majority of the patients, and there were some differences in this characteristic across the treatment groups. A slightly higher proportion of patients with new onset of localized headache were randomized to the TCZ arms. Symptoms of PMR appeared to be higher in the placebo arm with 52-week prednisone taper relative to the

[4] One randomized subject, WA28119-255730-11341, from the TCZ Q2W in combination with 26-week prednisone taper arm withdrew from the study the day the subject was randomized and did not receive any treatment. By protocol definition of the intent-to-treat (ITT) population, consisting of randomized patients receiving at least 1 dose, only 49 patients from TCZ Q2W with 26-week prednisone taper were included in the ITT analysis.

TCZ arms. These slight imbalances in disease characteristics are not unexpected due to the small sample sizes in each arm.

3.2.3.3 Other baseline GCA features

All patients presented with active GCA within 6 weeks of baseline. As in Table 5, baseline characteristics appeared to be balanced between treatment arms. On average, patients on the TCZ Q2W arm appeared to have higher CRP relative to patients on other arms, driven by two patients with CRP values greater than 90mg/L at diagnosis. On the other hand, patients randomized to the placebo arm with 26-week taper tended to have a higher average ESR relative to other groups.

There were some slight differences in baseline patient-reported outcomes (FACIT-Fatigue score, SF36 mental, SF36 physical, patient global assessment) across the treatment groups. Other key GCA disease characteristics appeared balanced across treatment groups.

3.2.3.4 Prednisone starting dose

Baseline prednisone dose categories were fairly balanced across treatment arms (See Table 6). Of note, one subject had the baseline prednisone dose imputed. The applicant clarified that since the blinded taper started at 20mg dose; it is "accurate to assume that these patients (or just one patient in this case) should fall into the ≤ 30mg/day group." A post-hoc rule was implemented for this patient who started on the blinded prednisone taper straight away to include the patient in the < 30mg group. This imputation was reasonable since data from Week 2 onwards were available to reliably impute the baseline value.

Table 3 Summary statistics of demographics and baseline anthropometric variables for all screened randomized subjects at baseline.

	PBO QW + 26-week prednisone taper (N=50)		PBO QW + 52-week prednisone taper (N=51)		TCZ QW + 26-week prednisone taper (N=100)		TCZ Q2W + 26-week prednisone taper (N=50)	
	n	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*
Age (years)	50	69 (8)	51	68 (8)	100	69 (9)	50	69 (8)
Age ≥ 65 years		34 (68%)		34 (67%)		68 (68%)		33 (66%)
Male	50	12 (24%)	51	14 (27%)	100	22 (22%)	50	15 (30%)
Ethnicity	50		51		100		50	
Hispanic or Latino		0 (0%)		1 (2%)		2 (2%)		1 (2%)
Not (Hispanic or Latino)		49 (98%)		49 (96%)		96 (96%)		46 (92%)
Not reported		0 (0%)		1 (2%)		2 (2%)		2 (4%)
Unknown		1 (2%)		0 (0%)		0 (0%)		1 (2%)
Race	50		51		100		50	
Asian		0 (0%)		0 (0%)		0 (0%)		1 (2%)
Black or African American		0 (0%)		2 (4%)		1 (1%)		0 (0%)
Other		0 (0%)		0 (0%)		1 (1%)		1 (2%)
Unknown		0 (0%)		0 (0%)		1 (1%)		1 (2%)
White		50 (100%)		49 (96%)		97 (97%)		47 (94%)
Weight (kg)	50	70.1 (15.8)	51	73.1 (15.3)	100	69.8 (13.8)	49	70.8 (16.1)
Height (cm)	50	165 (9.5)	51	168 (8.5)	100	164 (10.1)	49	165 (9.1)
BMI (kg/m^2)	50		51		100		49	
< 25		26 (52%)		25 (49%)		45 (45%)		26 (53%)
[25, 30)		14 (38%)		16 (31%)		39 (39%)		15 (31%)
≥ 30		10 (20%)		10 (20%)		16 (16%)		8 (16%)

[Source: Reviewer. Table 10 of CSR Module 5.3.5.1.]
Mean (SD) or Count (Percentage) is presented for continuous or dichotomous/categorical variables, respectively. Percentages are computed relative to the total number of randomized subjects (n) for the treatment arm. Sum of the percentages within the categories may not sum up to 100% due to rounding off errors.
Abbreviations: BMI=body mass index defined by weight divided by square of height (meters); PBO=placebo; SD=standard deviation; TCZ=tocilizumab; QW=every week; Q2W=every other week.

Table 4 Summary statistics of GCA disease features at diagnosis for all screened randomized subjects.

	PBO QW + 26-week prednisone taper (N=50)		PBO QW + 52-week prednisone taper (N=51)		TCZ QW + 26-week prednisone taper (N=100)		TCZ Q2W + 26-week prednisone taper (N=50)	
	n	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*
History of ESR > 50 mm/hour	50	49 (98%)	51	51 (100%)	100	94 (94%)	50	47 (94%)
History of CRP > 2.45 mg/dL	50	41 (82%)	51	38 (75%)	100	87 (87%)	50	43 (86%)
Presence of:								
New Onset Localized Headache	50	29 (58%)	51	34 (67%)	100	68 (68%)	50	38 (76%)
Scalp Tenderness	50	16 (32%)	51	16 (31%)	100	38 (38%)	50	20 (40%)
Temporal Artery Tenderness	50	14 (28%)	51	14 (27%)	100	26 (26%)	50	18 (36%)
Temporal Artery Decreased Pulsation	50	8 (16%)	51	6 (12%)	100	7 (7%)	50	8 (16%)
Ischemia-Related Vision Loss	50	7 (14%)	51	4 (8%)	100	7 (7%)	50	7 (14%)
Mouth or Jaw Pain Upon Mastication	50	20 (40%)	51	15 (29%)	100	31 (31%)	50	19 (38%)
Symptoms of PMR	50	30 (60%)	51	35 (69%)	100	59 (59%)	50	32 (64%)
TAB was performed	50	38 (76%)	51	33 (65%)	100	64 (64%)	50	37 (74%)
Positive TAB	38	36 (95%)	33	29 (88%)	64	57 (89%)	37	34 (92%)
Imaging study was performed	50	27 (54%)	51	27 (53%)	100	58 (58%)	50	27 (54%)
Type of imaging	27		27		58		27	
CTA		1 (4%)		1 (4%)		7 (12%)		4 (15%)
MRA		1 (4%)		0 (0%)		6 (10%)		1 (4%)
MRI		3 (11%)		1 (4%)		1 (2%)		1 (4%)
PET-CT		18 (67%)		21 (78%)		39 (67%)		19 (70%)
Other		4 (15%)		4 (15%)		5 (9%)		2 (7%)

[Source: Reviewer. Table 11 of CSR Module 5.3.5.1.]
Mean (SD) or Count (Percentage) is presented for continuous or dichotomous/categorical variables, respectively. Percentages are computed relative to the total number of randomized subjects (n) for the treatment arm. Sum of the percentages within the categories may not sum up to 100% due to rounding off errors.
Abbreviations: CRP=C-reactive protein; CTA=computed tomography angiography; ESR=erythrocyte sedimentation rate; MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; PBO=placebo; PET-CT=positron emission tomography-computed tomography angiography; PMR=polymyalgia rheumatic; SD=standard deviation; TCZ=tocilizumab; QW=every week; Q2W=every other week.

Table 5 Summary statistics of baseline GCA disease characteristics for all screened randomized subjects.

	PBO QW + 26-week prednisone taper (N=50)		PBO QW + 52-week prednisone taper (N=51)		TCZ QW + 26-week prednisone taper (N=100)		TCZ Q2W + 26-week prednisone taper (N=50)	
	n	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*
Active GCA within 6 Weeks of Baseline	50	50 (100%)	51	50 (98%)	100	100 (100%)	50	50 (100%)
Min number of days since GCA diagnosis	50	365 (569.8)	51	255 (435.5)	100	307 (563.5)	50	258 (500.7)
New GCA patients	50	23 (46%)	51	23 (45%)	100	47 (47%)	50	26 (52%)
CRP (mg/L)	50	7.7 (10.3)	51	8.2 (21.0)	100	6.8 (8.7)	49	11.4 (25.4)
ESR (mm/h)	50	28.8 (25.4)	51	24.2 (18.2)	99	24.6 (18.7)	49	20.8 (18.1)
Patient's Global VAS Assessment (mm)	49	35.7 (28.1)	51	47.8 (27.8)	100	43.6 (25.7)	49	46.7 (25.6)
EQ-5D-5L Score	50	0.74 (0.2)	49	0.66 (0.3)	99	0.74 (0.2)	49	0.74 (0.2)
FACIT-Fatigue Score	50	35.0 (12.8)	49	31.4 (13.6)	99	36.1 (11.1)	49	36.3 (11.5)
SF-36 Mental Component Summary	48	42.7 (12.1)	49	40.5 (13.7)	97	42.3 (12.4)	49	47.7 (12.6)
SF-36 Physical Component Summary	48	42.7 (10.9)	49	41.1 (10.0)	97	43.1 (9.4)	49	40.6 (8.0)
Signs and symptoms at diagnosis	50		51		100		50	
Cranial only		20 (40%)		16 (31%)		41 (41%)		18 (36%)
PMR only		10 (20%)		11 (22%)		22 (22%)		9 (18%)
Both cranial and PMR		20 (40%)		24 (47%)		37 (37%)		23 (46%)
Presence of:								
Fever (38°C or 100.4 F)	50	0 (0%)	51	0 (0%)	100	0 (0%)	50	0 (0%)
Ischemic optic neuropathy	50	0 (0%)	51	0 (0%)	100	1 (1%)	50	1 (2%)
Amaurosis fugax	50	0 (0%)	51	0 (0%)	100	1 (1%)	50	1 (2%)
Blurred vision	50	2 (4%)	51	5 (10%)	100	4 (4%)	50	3 (6%)
Diplopia	50	0 (0%)	51	0 (0%)	100	0 (0%)	50	0 (0%)
Bilateral blindness	50	0 (0%)	51	0 (0%)	100	0 (0%)	50	1 (2%)
Unilateral blindness	50	1 (2%)	51	1 (2%)	100	1 (1%)	50	1 (2%)

[Source: Reviewer.]
Mean (SD) or Count (Percentage) is presented for continuous or dichotomous/categorical variables, respectively. Percentages are computed relative to the total number of randomized subjects (n) for the treatment arm. Sum of the percentages within the categories may not sum up to 100% due to rounding off errors.
Abbreviations: CRP=C-reactive protein; EQ-5D= EuroQol five dimensions questionnaire; ESR=erythrocyte sedimentation rate; FACIT- Fatigue=Functional assessment of chronic illness therapy-fatigue (13-Item Scale); GCA=giant cell arteritis; PBO=placebo; PMR=polymyalgia rheumatic; SD=standard deviation; SF-36=short-form (36) health survey; TCZ=tocilizumab; QW=every week; Q2W=every other week; VAS=visual analog scale.

Table 6 Summary statistics of prednisone starting dose for all screened randomized subjects at baseline.

	PBO QW + 26-week prednisone taper (N=50)		PBO QW + 52-week prednisone taper (N=51)		TCZ QW + 26-week prednisone taper (N=100)		TCZ Q2W + 26-week prednisone taper (N=50)	
	n	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*
First Prednisone Dose (mg)[a]	50	34.6 (13.0)	51	34.5 (14.2)	100	34.6 (13.4)	49	35.9 (13.8)
Starting prednisone dose > 30 mg/day[a]	50	23 (46%)	51	25 (49%)	100	48 (48%)	50	25 (50%)
Starting prednisone dose categories	50		51		100		49	
20		12 (24%)		13 (25.5%)		26 (26.0%)		9 (18.4%)
25		4 (8%)		6 (11.8%)		5 (5.0%)		6 (12.2%)
30		11 (22%)		5 (9.8%)		19 (19.0%)		8 (16.3%)
35		4 (8%)		5 (9.8%)		6 (6.0%)		1 (2.0%)
40		9 (18%)		7 (13.7%)		20 (20.0%)		10 (20.4%)
50		4 (8%)		7 (13.7%)		11 (11.0%)		9 (18.4%)
60		6 (12%)		6 (11.8%)		11 (11.0%)		5 (10.2%)
Others		-		2 (3.9%)		2 (2.0%)		1 (2.0%)
First Steroid for GCA Dose (mg)	50	104.7 (197.9)	50	61.8 (44.9)	100	79.0 (143.9)	49	78.4 (150.7)

[Source: Reviewer.]
Mean (SD) or Counts (Percentage) are presented for continuous or categorical variables respectively.
[a]: One subject from TCZ QW with 26 week taper started on first blinded treatment wallet of 15mg/day prednisone. The applicant imputed the baseline prednisone starting dose based on the blinded treatment wallet.
Abbreviations: GCA=giant cell arteritis; PBO=placebo; SD=standard deviation; TCZ=tocilizumab; QW=every week; Q2W=every other week; VAS=visual analog scale.

3.2.4 Patient Disposition

A total of 83.6% of the randomized patients remained on their assigned double-blind treatment at the end of the study (See Table 7). The placebo arm with 52-week prednisone taper had the highest percentage of patients who remained on their randomized double-blind study agent and completed the study at Week 52. Patients on TCZ QW or TCZ Q2W arms had higher discontinuation rates from double-blind study agent (18% and 20% respectively) as well as study discontinuation rates (15% and 18% respectively) relative to the patients on the placebo arms. The cumulative incidence of subjects by treatment arm who discontinued study completely is shown in Figure 2. The cumulative incidence curves for study discontinuation for the TCZ arms appear to separate out more after Week 26 relative to the incidence curves of study discontinuation for the placebo arms.

Specific reasons for patients who discontinued double-blind study treatment are summarized in Table 8. The most common reason for treatment discontinuation on the TCZ QW arm was adverse event, followed by participant withdrawal without explicit reasons. There were similar

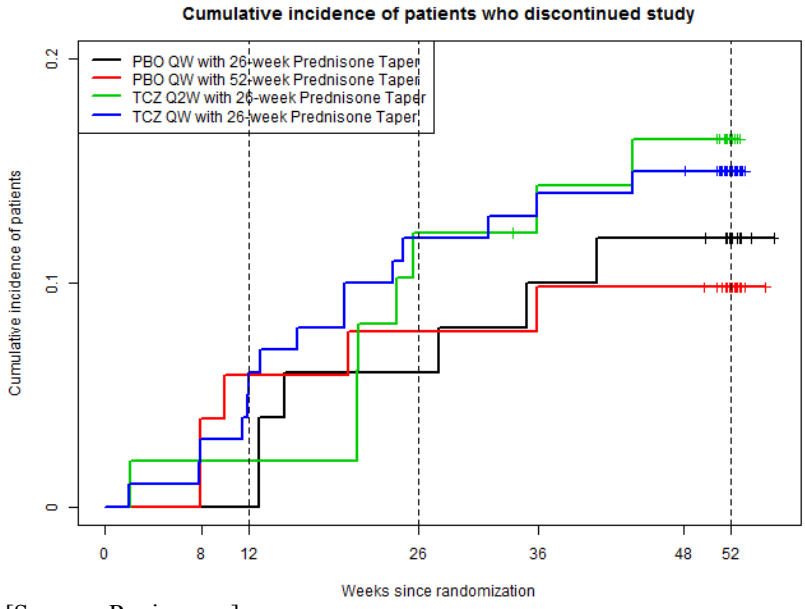
numbers of patients who discontinued treatment on the placebo with 26-week prednisone taper and TCZ Q2W dosing regimen arms for adverse events reasons.

Table 7 Disposition of patients at Week 52 in study WA28119 based on all randomized patients.

	PBO QW + 26-week prednisone taper (N=50)	PBO QW + 52-week prednisone taper (N=51)	TCZ QW + 26-week prednisone taper (N=100)	TCZ Q2W + 26-week prednisone taper (N=50)	Total
# who remained on double-blind study agent for 52 weeks[a]	41 (82%)	46 (90%)	82 (82%)	40 (80%)	209 (83%)
# who discontinued double-blind study agent[b]	9 (18%)	5 (10%)	18 (18%)	10 (20%)[c]	42 (17%)
ITT population (1)	*50*	*51*	*100*	*49*	*250*
# who remained in the study at 52 week (i)	*44 (88%)*	*46 (90%)*	*85 (85%)*	*40 (82%)*	*215 (86%)*
# who discontinued study completely (ii)	*6 (12%)*	*5 (10%)*	*15 (15%)*	*9 (18%)*	*35 (14%)*

[Source: Reviewer.]
(1) The total number of subjects in the final ITT dataset can be broken down into (i) and (ii). (i) & (ii) Figure 2 from CSR Module 5.3.5.1 differed by 1 subject who was lost to follow-up and counted as completing the 52-week study by the applicant. Percentages are relative to the ITT population (1).
[ab] : Table 7 from CSR Module 5.3.5.1. Percentages are relative to all randomized subjects (N) in the header.
[c] : This included the 1 patient who withdrew on the day of randomization.
Abbreviations: ITT=intent-to-treat based on all subjects with at least 1 dose of study agent; PBO=placebo; QW=every week; Q2W=every other week; TCZ=tocilizumab; #=number.

Figure 2 Cumulative incidence of patients who discontinue study completely over the 52-week study.



[Source: Reviewer.]
Abbreviations: PBO=placebo; QW=every week; Q2W=every other week; TCZ=tocilizumab.

Table 8 Summary of reasons for patients who discontinued double-blind study agent from Table 7 based on all ITT population.

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=50)[a]	Total
Total	9	5	18	9[a]	41
Safety	3		9	3	15
Adverse Event	3		9	3	15
Non-Safety	6	5	9	7	27
Lost to Follow-up					
Non-compliance			1[b]		1
Lack of Efficacy	1	2	1	3	7
Withdrawal by subject	2	1	5	2	10
Physician decision	3[c]	1[d]	1[e]	1[f]	6
Protocol Violation		1			1
Other			1[g]		1

[Source: Reviewer created disposition table. Table 7 from CSR Module 5.3.5.1.]
[a] : One patient who withdrew immediately after being randomized and did not start double-blind treatment were excluded.
[b] : Reason: "Patient will not take any study medication anymore."
[c] : Reasons included schedule for hip surgery, due to AE; due to flare and ineffectiveness of therapy.
[d] : Reason cited was due to elevated liver enzymes.
[e] : Reason cited was lack of efficacy.
[f] : Reason cited was flaring with anterior oschemic optic neuropathy (This is potentially flare related).
[g] : Reason cited was bilateral pneumonia.
Abbreviations: PBO=placebo; QW=every week; Q2W=every other week; TCZ=tocilizumab.

Table 9 Summary of reasons for patients who did not complete Week 52 visit from Table 7 based on ITT population.

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)	Total
Lack of Efficacy	2	2	1	3	8
Adverse Event	2		7	3	12
Withdrawal by Subject	2	1	6	2	11
Lost to Follow-up				1[a]	1
Protocol Violation		1			1
Physician decision		1[b]			1
Non-Compliance			1		1

[Source: Reviewer created disposition table.]
[a] : A subject is lost to follow up after clarification with the sponsor based on IR response on Feb 15 2017. Sensitivity analyses presented by the applicant treated this patient as a responder rather than as missing.
[b] : The physician decision was interpreted to be a hospitalization for a cardiac event.
Abbreviations: PBO=placebo; TCZ=tocilizumab; QW=every week; Q2W=every other week.

3.2.5 Results for WA28119

3.2.5.1 Primary efficacy endpoint of sustained remission at Week 52

The results for the primary and key secondary objectives are summarized in Table 10. Protocol-defined sustained remission from Week 12 through Week 52 was observed in 56 (56%; N=100) patients on the TCZ QW with 26-week prednisone taper arm, 26 (53.1%; N=49) patients in the TCZ Q2W with 26-week prednisone taper arm, 9 (18%; N=51) patients in the placebo with 52-week prednisone taper arm, and 7 (14%; N=50) patients in the placebo with 26-week prednisone taper arm.

Compared to the placebo with 26-week prednisone taper arm, patients randomized to TCZ QW with 26-week prednisone taper had a statistically significant 42% absolute increase (99.5% CI: 18% – 66%; p <0.0001) in the proportion achieving protocol-defined sustained remission from Week 12 through Week 52. Compared to the placebo with 26-week prednisone taper arm, patients randomized to TCZ Q2W arm with 26-week prednisone taper had a statistically significant 39% absolute increase (99.5% CI: 12% - 66%; p<0.0001) in the proportion of protocol-defined sustained remission from Week 12 through Week 52.

Compared to the placebo with 52-week prednisone taper, patients on the TCZ QW arm with 26-week prednisone taper had a statistically significant 38% absolute increase (99.5% CI: 14% – 62%; p <0.0001) in the proportion of protocol-defined sustained remission from Week 12 through Week 52. Compared to the placebo with 52-week prednisone taper, patients on TCZ Q2W with 26-week prednisone taper had a statistically significant 35% absolute increase (99.5% CI: 9% - 62%; p<0.0001) in the proportion of protocol-defined sustained remission from Week 12 through Week 52.

Additional sensitivity analyses that excluded the additional non-responder imputation for patients with elevated CRP followed by a missing consecutive visit did not affect any of these findings. Further sensitivity analyses that considered to be non-responders a total of three subjects who were responders for the protocol-defined sustained remission endpoint and were followed to the end of the study but discontinued double-blind treatment prior to Week 52 (two subjects from the placebo arm with 26-week prednisone taper and one subject from TCZ QW) also did not affect the key findings.

3.2.5.1.1 Sensitivity analysis based on individual components of composite endpoint

Results for the sensitivity analyses based on the individual components of sustained remission are included in Table 10. The comparison with the control arm that most appropriately represents standard of care, the placebo arm with 52-week prednisone taper, is of critical interest to provide further evidence of efficacy of TCZ.

Sustained remission based only on the absence of signs and symptoms of GCA from Week 12 through Week 52 was observed in 23 (45%; N=51) patients on placebo with 52-week prednisone taper, 20 (40%; N=50) patients on placebo arm with 26-week prednisone taper, 69 (69%; N=100) patients on TCZ QW with 26-week prednisone taper, and 28 (57%; N=49) patients on

TCZ Q2W with 26-week prednisone taper. The proportions of responders, based on the individual components of sustained remission, are higher in the placebo arms because this refined definition of sustained remission is independent of other components.

Compared to the placebo arm with 52-week prednisone taper, the estimated proportion of patients on the TCZ QW arm with 26-week prednisone taper achieving sustained absence of signs or symptoms of GCA from Week 12 through Week 52 was 24% higher on the absolute scale (99.5% CI: 0.3% - 47%; p =0.00465). Although the treatment effect based on absence of signs or symptoms of GCA alone was attenuated towards the null relative to the results for the primary composite remission endpoint, this difference of 23% is considered clinically meaningful and the corresponding hypothesis test rejected the null hypothesis of no difference between the treatment arms.

Compared to the placebo with 52-week prednisone taper, the estimated proportion of patients on the TCZ Q2W arm with 26-week prednisone taper achieving sustained absence of signs or symptoms of GCA from Week 12 through Week 52 was 12% higher on the absolute scale (99.5% CI: 16% lower - 40% higher; p=0.23). This estimated treatment effect is attenuated more sharply towards the null hypothesis of no difference between the TCZ Q2W and placebo with 52-week prednisone taper arms, and the difference was not statistically significant. The evidence of benefit for the TCZ Q2W arm with 26-week prednisone taper relative to the placebo arm with 52-week prednisone taper is less convincing than the evidence for the more frequent QW TCZ dosing arm despite a numerical trend of the TCZ Q2W arm towards benefit.

As shown in Table 11, the proportions of patients with sustained absence of GCA signs and symptoms from Week 12 through various time points were higher for TCZ QW relative to placebo with 52-week prednisone taper as well as placebo with 26-week prednisone taper. This was similarly observed for TCZ Q2W relative to the placebo arms. The proportions of patients with absence of GCA signs and symptoms at specific visits are shown in Table 12.

In summary, the evidence for the proposed dosing regimen of TCZ QW demonstrated compelling evidence across various key primary and critical sensitivity analyses based on the individual components. The efficacy for TCZ Q2W with 26-week prednisone taper was compelling for the protocol-defined composite primary endpoint, but was less convincing in analyses focusing on only signs and symptoms of GCA, without the influence of effects on inflammatory markers and steroid taper adherence. The results based on the individual component of signs and symptoms along from Week 12 through Week 52 also provide some quantitative evidence of a dose response, with a trend suggesting that the TCZ QW dosing may lead to a higher probability of response relative to the TCZ Q2W dosing.

3.2.5.1.2 Sensitivity analyses to address the potential effect of missing data

The applicant conducted a tipping point sensitivity analysis to address the degree to which violations in assumptions about patients who discontinued the study completely might affect results for the primary endpoint of sustained remission. The applicant's analysis varied the outcomes of patients who did not have induced remission or have flares prior to discontinuing the study. In total, two patients from the placebo arm with 26-week prednisone taper, three from

the placebo arm with 52-week prednisone taper, 14 from the TCZ QW with 26-week taper, and five from the TCZ Q2W with 26-week taper arms, who had induced remission at Week 12 and were still in sustained remission at the time they discontinued from the study completely or were lost to follow up, were included in the tipping point analysis. These sensitivity analyses further demonstrated robustness of the primary endpoint results (results not shown).

Of the 35 subjects who discontinued from the study prior to Week 52, four from placebo with 26-week prednisone taper, three from placebo with 52-week prednisone taper, thirteen from TCZ QW with 26-week prednisone taper, and four from TCZ Q2W with 26-week prednisone taper had not had signs or symptoms of GCA at the time of discontinuation from the study. I conducted an analogous sensitivity analysis by exploring the possible outcomes of the responder status of these 24 subjects who did not complete the Week 52 follow up (See Table 7) based on sustained remission defined only by the absence of signs or symptoms of GCA, using a conservative unadjusted 99.5% CI.

For example, in the top left heatmap of Figure 3, at the coordinate (x-axis=0, y-axis=0), the results represent the scenario in which all subjects who discontinued from the study were non-responders. Of note, the majority of the plausible outcomes conclude superiority of TCZ QW with 26-week prednisone taper relative to the placebo with 52-week prednisone taper at the 2-sided level of 0.5%. The worst-case assumption for the evaluation of TCZ QW with 26-week prednisone taper would be at coordinate (3, 0), in which all placebo patients are responders while no patients on TCZ QW with 26-week prednisone taper are responders. Even in this conservative scenario, the tipping point analysis provides statistical evidence of superiority for TCZ QW with 26-week prednisone taper relative to placebo with 52-week taper (with a difference in response probabilities of roughly 20%), albeit at the typical two-sided 5% level rather than the more stringent 0.5% level utilized in the primary analysis.

Table 10 Analyses of primary endpoint and sensitivity analyses of individual components of composite primary endpoint comparing tocilizumab (TCZ) dosing regimens with the placebo (PBO) with 26-week prednisone taper and placebo with 52-week prednisone taper arms.

	PBO QW + 26-week Prednisone Taper (N=50)	**PBO QW + 52-week Prednisone Taper (N=51)**	**TCZ QW + 26-week Prednisone Taper (N=100)**	**TCZ Q2W + 26-week Prednisone Taper (N=49)**
Protocol-defined sustained remission	7 (14%)	9 (18%)	56 (56%)	26 (53%)
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			42% (18%, 66%)	39% (12%, 66%)
p-value			<0.0001	<0.0001
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			38% (14%, 62%)	35% (9%, 62%)
p-value			<0.0001	0.0002
Individual components of sustained remission				
Absence of signs and symptoms of GCA[a]	20 (40%)	23 (45%)	69 (69%)	28 (57%)[a]
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			29% (5%, 53%)	17% (-11%, 45%)
p-value			0.0007	0.0968
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			24% (0.3%, 47%)	12% (-16%, 40%)
p-value			0.0046	0.2344
Absence of elevated ESR attributable to GCA[a]	20 (40%)	22 (43%)	83 (83%)	37 (76%)[a]
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			43% (20%, 66%)	36% (8%, 63%)
p-value			<0.0001	0.00045
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			40% (18%, 62%)	32% (5%, 60%)
p-value			<0.0001	0.0010
Normalization of CRP[a]	17 (34%)	13 (25%)	72 (72%)	34 (69%)[a]
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			38% (14%, 62%)	35% (7%, 64%)
p-value			<0.0001	0.0005
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			47% (23%, 70%)	44% (16%, 72%)
p-value			<0.0001	<0.0001
Successful prednisone tapering	10 (20%)	20 (39%)	60 (60%)	28 (57%)
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			40% (16%, 64%)	37% (10%, 65%)
p-value			<0.0001	0.0002
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			21% (-3%, 45%)	18% (-10%, 46%)
p-value			0.0160	0.0742

[Source: Reviewer created above table using STATA 14.0.]

[a] : Reviewer results differ from the applicant's IR response due to (1) P-values computed by the applicant did not stratify by baseline prednisone category; (2) Reviewer accounted for an additional subject lost to follow-up who should have been considered a non-responder in applicant analyses.

Abbreviations: CI=confidence intervals; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; QW=every week; Q2W=every other week.

Table 11 Percentage of patients with induction of remission at Week 12, defined by absence of signs and symptoms of GCA at Week 12, and sustained absence of signs and symptoms of GCA from Week 12 until various weeks (up to Week 52), regardless of ESR level, CRP level, and adherence to the steroid taper.

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Responders at Week 12	43 (86.0%)	38 (74.5%)	93 (93.0%)	43 (87.8%)
Sustained responders at Week 16	38 (76.0%)	36 (70.6%)	87 (87.0%)	41 (83.7%)
Sustained responders at Week 20	36 (72.0%)	32 (62.7%)	83 (83.0%)	37 (75.5%)
Sustained responders at Week 24	30 (60.0%)	27 (52.9%)	79 (79.0%)	33 (67.3%)
Sustained responders at Week 28	26 (52.0%)	27 (52.9%)	78 (78.0%)	32 (65.3%)
Sustained responders at Week 32	25 (50.0%)	27 (52.9%)	75 (75.0%)	32 (65.3%)
Sustained responders at Week 36	22 (44.0%)	26 (51.0%)	72 (72.0%)	29 (59.2%)
Sustained responders at Week 40	21 (42.0%)	25 (49.0%)	71 (71.0%)	29 (59.2%)
Sustained responders at Week 44	20 (40.0%)	25 (49.0%)	71 (71.0%)	29 (59.2%)
Sustained responders at Week 48	20 (40.0%)	25 (49.0%)	70 (70.0%)	29 (59.2%)
Sustained responders at Week 52	20 (40.0%)	23 (45.1%)	69 (69.0%)	28 (57.1%)
Missing between Week 12 and 16	3 (6.0%)	3 (5.9%)	9 (9.0%)	1 (2.0%)
Missing between Week 12 and 20	3 (6.0%)	4 (7.8%)	10 (10.0%)	1 (2.0%)
Missing between Week 12 and 24	3 (6.0%)	4 (7.8%)	11 (11.0%)	5 (10.2%)
Missing between Week 12 and 28	4 (8.0%)	4 (7.8%)	12 (12.0%)	6 (12.2%)
Missing between Week 12 and 32	4 (8.0%)	4 (7.8%)	12 (12.0%)	6 (12.2%)
Missing between Week 12 and 36	5 (10.0%)	5 (9.8%)	14 (14.0%)	8 (16.3%)
Missing between Week 12 and 40	6 (12.0%)	5 (9.8%)	14 (14.0%)	8 (16.3%)
Missing between Week 12 and 44	6 (12.0%)	5 (9.8%)	15 (15.0%)	9 (18.4%)
Missing between Week 12 and 48	6 (12.0%)	5 (9.8%)	15 (15.0%)	9 (18.4%)
Missing between Week 12 and 52	6 (12.0%)	5 (9.8%)	15 (15.0%)	9 (18.4%)

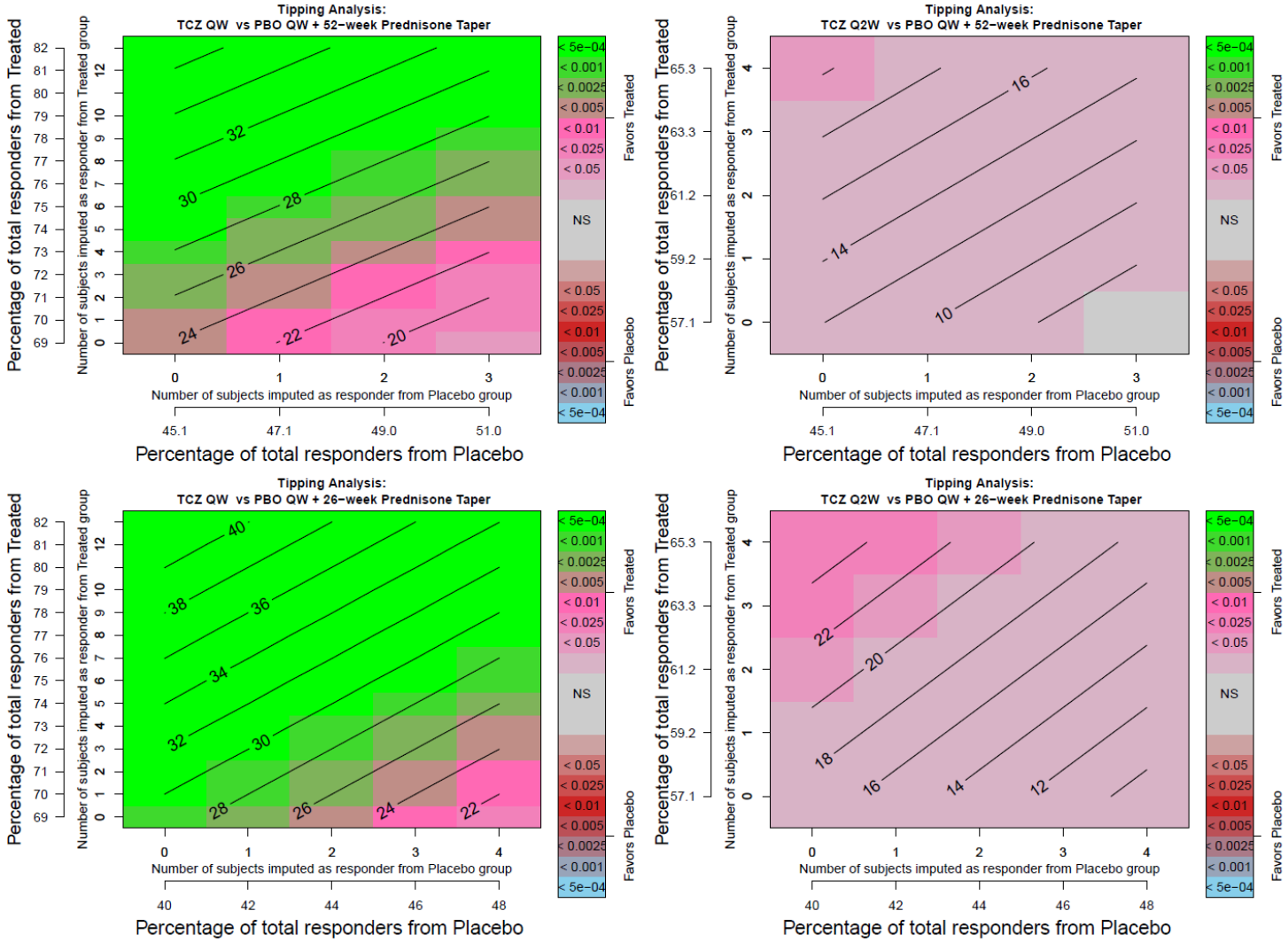
[Source: t-ef-gca-sust-fda2; Reviewer modified the script to account for an additional subject lost to follow-up and thus should be classified as missing from Week 36 onwards.]
Counts and percentages were presented.
Abbreviations: CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; PBO=placebo; QW=every week; Q2W= every other week; TCZ=tocilizumab.

Table 12 Cross-sectional analyses of the total number and proportion of patients with an absence of signs and symptoms of GCA at each visit week, regardless of ESR level, CRP level, and adherence to the steroid taper.

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Responders at Week 12	43 (86.0%)	38 (74.5%)	93 (93.0%)	43 (87.8%)
Responders at Week 16	41 (82.0%)	40 (78.4%)	88 (88.0%)	42 (85.7%)
Responders at Week 20	42 (84.0%)	39 (76.5%)	86 (86.0%)	41 (83.7%)
Responders at Week 24	38 (76.0%)	36 (70.6%)	84 (84.0%)	38 (77.6%)
Responders at Week 28	40 (80.0%)	39 (76.5%)	88 (88.0%)	40 (81.6%)
Responders at Week 32	40 (80.0%)	39 (76.5%)	85 (85.0%)	39 (79.6%)
Responders at Week 36	38 (76.0%)	42 (82.4%)	84 (84.0%)	35 (71.4%)
Responders at Week 40	39 (78.0%)	42 (82.4%)	83 (83.0%)	38 (77.6%)
Responders at Week 44	39 (78.0%)	42 (82.4%)	85 (85.0%)	39 (79.6%)
Responders at Week 48	40 (80.0%)	38 (74.5%)	84 (84.0%)	39 (79.6%)
Responders at Week 52	39 (78.0%)	36 (70.6%)	83 (83.0%)	37 (75.5%)

[Source: t-ef-gca-resp-fda2.sas; Reviewer modified the script to account for an additional subject from TCZ Q2W who was lost to follow-up and thus classified as missing from Week 36 onwards.]
Counts and percentages were presented.
Abbreviations: CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; QW=every week; Q2W=every other week; GCA=giant cell arteritis; PBO=placebo; TCZ=tocilizumab.

Figure 3 Tipping point analysis for sustained remission defined by sustained absence of signs and symptoms of GCA from Week 12 through Week 52, regardless of ESR level, CRP level, adherence to the steroid taper, and adherence to study drug, comparing tocilizumab (TCZ) arms to placebo (PBO) arms.



[Source: Reviewer.] Assumptions were varied for the outcomes in patients who discontinued the study. P-values are unadjusted for baseline prednisone category. (0, 0) represent the observed estimated treating who did not complete Week 52 visit as non-responders in Table 10.
Abbreviations: CI=confidence interval; PBO=placebo; QW=every week; Q2W= every other week; SD=standard deviation; TCZ=tocilizumab.

3.2.5.2 Patient-reported outcomes

The results based on the regression analysis at each visit week are presented in Table 13 and Table 14. Even though these endpoints were not controlled for multiplicity and were considered exploratory, these analyses are important as part of the totality of evidence supporting effectiveness, given that they are direct measures of how patients function and feel.

3.2.5.2.1 Key findings for components of SF-36

There was statistical evidence suggesting a greater change from baseline in the SF-36 mental and SF36 physical component summary scores on TCZ QW relative to the placebo arm with 52-week prednisone taper at week 52. On average, at Week 52, for any patient with similar baseline SF-36 mental score, baseline prednisone category, and values of other adjustment covariates, the mean change from baseline in the SF-36 mental component score is estimated to be 6.2 points higher (99% CI: 2.2, 10.3; $p<0.001$) on TCZ QW as compared to the placebo arm with 52-week taper. Similarly, for the SF-36 physical component score, the mean change from baseline in the SF-36 physical component is estimated to be 4.6 points higher (99% CI: 1.1, 8.0; $p<0.001$) on TCZ QW than placebo with 52-week prednisone taper. At earlier weeks (e.g., 12 and 24), there was a lack of clear numerical trends toward improvement on TCZ for both the SF-36 physical and mental component scores. Trends toward improvements in the SF-36 mental score were noted from Week 36 through Week 52 while improvement in the SF-36 physical score was noticeable by Week 48.

Evidence of improvements in the two key components of SF-36 was less convincing for TCZ Q2W with 26-week prednisone taper relative to the placebo arm with 52-week prednisone taper. Numerical trends of improvements from baseline relative to the placebo arm with 52-week prednisone taper were generally smaller in magnitude than those observed for TCZ QW.

3.2.5.2.2 Key findings for patient VAS assessment

There was statistical evidence suggesting a greater change from baseline in the patient VAS assessment score on TCZ Q2W relative to placebo with 52-week prednisone taper. The mean change from baseline in patient global VAS assessment score at Week 52 was on average 14.4 points lower (99% CI: -27.7, -1.1; $p=0.0054$) for any patient with similar baseline global VAS score, baseline prednisone category, and values of other adjustment covariates, comparing the TCZ Q2W arm relative to the placebo arm with 52-week prednisone taper. The change from baseline in patient VAS assessment score was estimated to be 9.6 points greater on the TCZ QW arm relative to the placebo arm with 52-week taper, although the upper limit of the 99% confidence interval did not exclude zero (99% CI: -21.0, +1.8; $p=0.0299$). Results over time were generally similar for both TCZ doses, with trends toward improvement versus the placebo arms most evident at later time points in the study.

Table 13 Summary of mean of the baseline value, mean of the change from baseline post baseline, and number of available measurements, for SF-36 mental and physical component summary scores, based on all observed data in all randomized subjects regardless of escape. Regression results are presented in the last four columns.

		PBO QW + 26-week Prednisone Taper		PBO QW + 52-week Prednisone Taper		TCZ QW + 26-week Prednisone Taper		TCZ Q2W + 26-week Prednisone Taper		TCZ QW vs PBO QW + 26-week Prednisone Taper Estimated Difference (99% CI); p-value	TCZ Q2W vs PBO QW + 26-week Prednisone Taper Estimated Difference (99% CI); p-value	TCZ QW vs PBO QW + 52-week Prednisone Taper Estimated Difference (99% CI); p-value	TCZ Q2W vs PBO QW + 52-week Prednisone Taper Estimated Difference (99% CI); p-value
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)				
Mental Component Score	Baseline Mean	48	42.7 (12.1)	49	40.5 (13.7)	97	42.8 (12.4)	49	47.7 (12.6)				
	Week 12	47	3.9 (12.8)	49	5.4 (10.4)	94	6.6 (10.0)	49	2.5 (14.1)	2.9 (-1.5,7.2); 0.0854	1.4 (-3.6,6.5); 0.4552	2.5 (-1.8,6.9); 0.1258	1.1 (-3.9,6.1); 0.5701
	Week 24	45	6.5 (12.9)	44	6.8 (11.8)	88	6.1 (12.2)	46	3.3 (11.9)	-0.3 (-4.6,4.0); 0.8642	0.2 (-4.7,5.2); 0.8964	0.9 (-3.5,5.2); 0.6066	1.4 (-3.6,6.4); 0.4725
	Week 36	42	6.5 (13.0)	45	5.1 (10.1)	82	9.7 (11.5)	42	2.9 (10.9)	2.8 (-1.5,7.1); 0.0922	-0.2 (-5.2,4.8); 0.9356	5.1 (0.9,9.4); 0.0020	2.2 (-2.8,7.1); 0.2623
	Week 48	41	5.2 (12.0)	43	5.0 (11.4)	80	7.6 (12.3)	40	4.6 (10.3)	3.2 (-1.2,7.6); 0.0614	3.6 (-1.6,8.7); 0.0736	4.3 (-0.1,8.7); 0.0122	4.6 (-0.5,9.8); 0.0202
	Week 52	41	6.1 (11.8)	43	3.3 (12.4)	82	9.1 (10.7)	39	4.3 (9.5)	2.8 (-1.3,7.0); 0.0727	1.3 (-3.5,6.1); 0.4751	6.2 (2.2,10.3); <0.001	4.7 (-0.1,9.5); 0.0115
Physical Component Score	Baseline Mean	48	42.6 (10.9)	49	41.1 (10.0)	97	43.1 (9.4)	49	40.6 (8.0)				
	Week 12	47	-0.5 (8.6)	49	1.1 (6.6)	94	2.1 (7.9)	49	1.0 (6.6)	2.8 (-0.5,6.1); 0.0299	0.9 (-2.9,4.7); 0.5253	1.6 (-1.7,4.9); 0.2065	-0.3 (-4.0,3.5); 0.8585
	Week 24	45	-0.0 (8.6)	44	2.9 (6.3)	88	2.0 (8.9)	46	-0.8 (7.7)	1.7 (-1.9,5.2); 0.2226	-1.6 (-5.7,2.5); 0.3091	-0.1 (-3.7,3.5); 0.9472	-3.4 (-7.4,0.7); 0.0326
	Week 36	42	1.1 (8.8)	45	2.2 (7.1)	82	1.7 (6.8)	42	-1.3 (7.2)	0.5 (-2.9,3.8); 0.7154	-2.6 (-6.5,1.3); 0.0800	0.0 (-3.3,3.3); 0.9845	-3.1 (-6.9,0.7); 0.0374
	Week 48	41	0.0 (8.1)	43	-0.1 (7.2)	80	2.9 (7.7)	40	0.6 (8.5)	2.6 (-1.0,6.2); 0.0590	0.3 (-3.9,4.4); 0.8548	3.4 (-0.2,6.9); 0.0141	1.1 (-3.0,5.1); 0.5016
	Week 52	41	-1.3 (8.4)	43	0.3 (8.1)	82	4.2 (7.6)	39	2.8 (8.7)	5.2 (1.7,8.7); <0.001	3.2 (-0.8,7.3); 0.0399	4.6 (1.1,8.0); <0.001	2.7 (-1.3,6.7); 0.0865

[Source: Reviewer. The table format was revised based on sponsor submitted program t-ef-cb-repm.txt.]
Abbreviations: CI=confidence interval; PBO=placebo; QW=every week; Q2W= every other week; SD=standard deviation; SF-36=short-form 36; TCZ=tocilizumab.

Table 14 Mean baseline patient global VAS assessment score, mean change from baseline in patient global VAS assessment score post baseline and number of available data were summarized based on all observed randomized subjects regardless of escape. Regression results were presented on the last four columns.

	PBO QW + 26-week Prednisone Taper		PBO QW + 52-week Prednisone Taper		TCZ QW + 26-week Prednisone Taper		TCZ Q2W + 26-week Prednisone Taper		TCZ QW vs PBO QW + 26-week Prednisone Taper Estimated Difference (99% CI); p-value	TCZ Q2W vs PBO QW + 26-week Prednisone Taper Estimated Difference (99% CI); p-value	TCZ QW vs PBO QW + 52-week Prednisone Taper Estimated Difference (99% CI); p-value	TCZ Q2W vs PBO QW + 52-week Prednisone Taper Estimated Difference (99% CI); p-value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)				
Baseline Mean	49	35.7 (28.1)	51	47.8 (27.8)	100	43.6 (25.7)	49	46.7 (25.6)				
Week 12	48	-4.8 (32.4)	51	-14.1 (22.5)	96	-14.4 (25.2)	49	-10.3 (28.7)	-5.1 (-15.0,4.9) 0.1900	0.9 (-10.6,12.4) 0.8437	-2.7 (-12.5,7.0) 0.4694	3.2 (-8.0,14.5) 0.4599
Week 24	46	2.4 (27.8)	47	-17.0 (27.8)	90	-11.6 (27.8)	46	-11.3 (28.2)	-11.1 (-22.1,-0.1) 0.0096	-8.1 (-20.8,4.6) 0.0989	1.5 (-9.4,12.4) 0.7292	4.4 (-8.1,17.0) 0.3604
Week 36	45	-1.8 (27.0)	46	-15.0 (30.8)	87	-15.9 (30.5)	41	-15.0 (23.5)	-9.3 (-20.7,2.0) 0.0341	-7.5 (-20.8,5.8) 0.1430	-4.2 (-15.4,7.0) 0.3305	-2.4 (-15.5,10.7) 0.6324
Week 48	43	-4.3 (30.3)	46	-11.1 (33.0)	84	-16.3 (32.6)	41	-17.8 (26.4)	-7.2 (-19.1,4.8) 0.1203	-7.3 (-21.2,6.6) 0.1744	-9.6 (-21.3,2.1) 0.0345	-9.7 (-23.3,3.9) 0.0657
Week 52	43	-3.0 (27.6)	43	-13.2 (32.3)	85	-17.6 (30.2)	40	-23.7 (24.2)	-9.9 (-21.4,1.6) 0.0256	-14.8 (-28.2,-1.3) 0.0049	-9.6 (-21.0,1.8) 0.0299	-14.4 (-27.7,-1.1) 0.0054

[Source: Reviewer. The table format was revised based on sponsor submitted program t-ef-cb-repm.txt.]
Abbreviations: CI=confidence interval; PBO=placebo; QW=every week; Q2W= every other week; SD=standard deviation; TCZ=tocilizumab; VAS=visual analogue scale.

3.2.5.3 Cumulative prednisone dose over the course of the study

The evaluation of cumulative prednisone use over the course of the study is important to further characterize the benefits of tocilizumab in treating GCA. The results in this section first describe the amount of study follow-up for the subjects, followed by the proportion of patients who escaped, and then the descriptive results of cumulative prednisone use over time.

3.2.5.3.1 Duration of follow-up and exposure to double-blind study agent

The mean duration of follow-up across the treatment arms were in general similar (Table 15). The average exposure to the double-blind study agent was slightly longer on the placebo arms than the TCZ arms.

Table 15 A summary of study follow-up during the double-blind period in person years (PY).

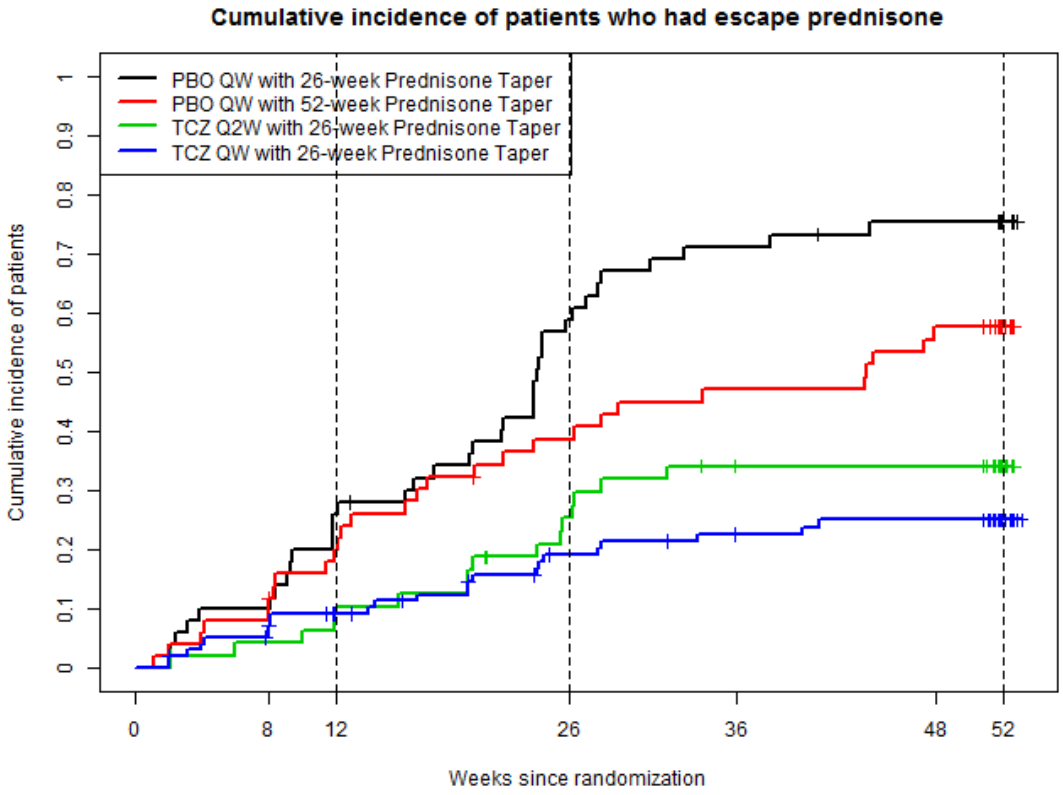
	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Duration of Follow-Up				
Mean	0.95	0.94	0.93	0.93
Median	1.00	1.00	1.00	1.00
Minimum – Maximum	0.29 - 1.03	0.16 - 1.02	0.16 - 1.02	0.31 - 1.02
Total follow-up (PY)	47.44	48.06	92.89	45.57
Exposure to study agent				
Mean	0.89	0.90	0.86	0.89
Minimum – Maximum	0.13 - 1.02	0.13 - 1.02	0.04 - 1.02	0.04 - 1.02
Total exposure (PY)	44.33	46.03	86.41	43.70

[Source: Reviewer created table.]
Abbreviations: PBO=placebo; QW=every week; Q2W=every other week; TCZ=tocilizumab.

3.2.5.3.2 Patients who had escape prednisone

The cumulative incidence of patients who moved to escape prednisone over the course of the study is summarized in Figure 4. A total of 104 subjects had escape prednisone over the entire course of the study. There was greater use of escape prednisone on the placebo arms than the TCZ arms: 37 (74%) patients used escape prednisone on placebo with 26-week prednisone taper, 28 (55%) on placebo with 52-week prednisone taper, 16 (33%) on TCZ Q2W with 26-week prednisone taper, and 23 (23%) on the TCZ QW arm with 26-week prednisone taper. Based on Figure 4, the cumulative incidence curves for patients randomized to the placebo arms ([black] and [red] curves) separate out distinctly from the cumulative incidence curves for patients randomized to the TCZ arms ([blue] and [green] curves). This separation started at roughly 8 weeks after randomization and persisted until the end of the study.

Figure 4 Kaplan Meier curve of the proportion of patients who were moved to escape prednisone.



[Source: Reviewer created graph.]
Patients who were censored at the last follow-up date in the study were marked with cross-hairs.
Abbreviations: PBO=placebo; QW=every week; Q2W=every other week; TCZ=tocilizumab.

Among patients randomized to placebo (either with 26-week prednisone taper [black] or with 52-week prednisone taper [red]), the cumulative incidence of patients requiring escape did not differ much prior to week 26. Around week 26, the two cumulative incidence curves began to separate with an increase in the number of patients requiring escape prednisone on the placebo arm with the shorter 26-week taper. Such observations are consistent with previously stated Agency concerns that patients on the shorter taper may be under-treated for their disease relative to the 52-week taper (a better representation of standard of care).

Among patients randomized to TCZ (either QW [blue] or Q2W [green] dose), the cumulative incidence of patients requiring escape prednisone appeared similar prior to week 26 during the planned steroid taper. After week 26, the TCZ Q2W arm was observed to have a slight increase in the proportion of subjects requiring escape prednisone relative to the QW arm.

3.2.5.3.3 Adjusted total prednisone dose

The applicant's summary statistics of total prednisone dose up to last visit are shown in Table 16. Summary statistics for the cumulative prednisone dose were computed up to a subject's last observed total prednisone use over the 52-week study. As shown in Table 16, the last

cumulative prednisone dose tended to be roughly two times lower for the TCZ QW arm relative to the placebo arms. Furthermore, the maximum cumulative prednisone dose was also much lower on the TCZ QW arm relative to the placebo arms.[5] There were several patients on the TCZ Q2W arm who had a considerably higher total prednisone use than the maximum dose observed among subjects on TCZ QW.

Table 16 Summary statistics based on the last observed cumulative prednisone dose in the study.

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Mean (SD)	3765 (2022.5)	4199 (2291.3)	2098 (1248.5)	2447 (1827.3)
Geometric Mean	3255	3631	1803	1997
Median	3296	3818	1862	1862
Minimum – Maximum	932.0 – 9777.5	822.5 – 10697.5	630.0 – 6602.5	295.0 – 9912.5

[Source: Reviewer.]
Subjects' last observed cumulative prednisone dose was used to produce the summary statistics above.
Abbreviations: PBO=placebo; QW=every week; Q2W=every other week; SD=standard deviation; TCZ=tocilizumab.

The analysis of cumulative prednisone dose by the applicant presents various interpretation issues when patients discontinued from the study prior to Week 52. As noted in 3.2.4, approximately 14% of the subjects were not followed through Week 52. The applicant presented cumulative prednisone dose through the time of dropout in patients who withdrew from the study. Limitations of this analysis were discussed previously in 3.2.2.2.

Cumulative adjusted annual total prednisone doses were highest on the placebo arm with 52-week taper, and were considerably lower on the TCZ arms relative to the placebo arms, as shown in Table 17. The estimated geometric mean total prednisone dose adjusted for study follow-up was 50% lower on the TCZ QW arm relative to the placebo arm with 52-week taper (99% CI 40% lower to 58% lower), on the relative scale. The estimated geometric mean total prednisone dose adjusted for study follow-up was 47% lower on the TCZ QW arm relative to the placebo arm with 52-week taper (99% CI 34% lower to 57% lower).

[5] The sampling distribution of the maximum depends on the sample size of the treatment arm.

Table 17 Summary statistics based on the total annual prednisone dose adjusted for study follow-up and results from a linear regression, allowing for heteroskedasticity, comparison with placebo arms.

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Mean (SD)	4049 (2084.8)	4469 (2205.7)	2327 (1303.1)	2618 (1818.4)
Geometric Mean	3524	4022	2028	2199
Median	3804	3902	1887	2207
Minimum – Maximum	935.2 – 10174.4	2166.4 – 10704.8	812.6 – 6607.0	949.4 – 9838.4
Vs PBO with 26-week Ratio of geometric means 99% CI			0.57 (0.467 - 0.699)	0.61 (0.477 - 0.769)
Vs PBO with 52-week Ratio of geometric means 99% CI			0.50 (0.428 - 0.591)	0.53 (0.434 - 0.656)

[Source: Reviewer.]
Abbreviations: PBO=placebo; Q1=25th quantile; Q3=75th quantile; SD=standard deviation; TCZ=tocilizumab.

3.3 Evaluation of Safety

Infections are common known side effects of use of immunosuppressive therapy. In this limited safety review, I included a brief summary of the adverse events related to infections in this study.

3.3.1 Infections

The rates of infection per 100 PY were similar between the TCZ QW with 26-week prednisone taper and placebo with 52-week prednisone taper arms as shown in Table 18. In addition, the infection rates were also similar between the TCZ Q2W with 26-week prednisone taper and placebo with 26-week prednisone taper arms; rates in these arms were slightly lower than the other two arms. Serious infection rates were also higher on the TCZ QW with 26-week prednisone taper and placebo with 52-week prednisone taper arms than both the TCZ Q2W with 26-week prednisone taper and placebo with 26-week prednisone taper arms (which were similar).

Serious infections rates were highest on the placebo arm with 52-week prednisone taper. There is considerable uncertainty around the comparisons between treatment arms for these events due to the small sample sizes and numbers of events. Nevertheless, it is reassuring that rates of infections, an adverse event that is commonly associated with immunosuppressant therapies such as TCZ, were comparable between the TCZ QW and placebo with 52-week taper arms.

The reader is referred to the review conducted by the Medical Reviewer, Dr. Glaser, for a more comprehensive evaluation of the safety of the proposed doses of tocilizumab for patients with GCA.

Table 18 Adverse events that were related to infections or serious infections reported during the study.

	PBO QW + 26-week Prednisone Taper (n=50)	PBO QW + 52-week Prednisone Taper (n=51)	TCZ QW + 26-week Prednisone Taper (n=100)	TCZ Q2W + 26-week Prednisone Taper (n=49)
Total study follow-up	47.4	48.1	92.9	45.6
Subjects with any infections[a] (n)	38 (76%)	33 (65%)	75 (75%)	36 (73%)
Total infections (Rate[b])	74 (156.0)	101 (210.2)	186 (200.2)	73 (160.2)
Subjects with serious infections[a] (n)	2 (4%)	6 (12%)	7 (7%)	2 (4%)
Total serious infections (Rate[b])	2 (4.2)	6 (12.5)	9 (9.7)	2 (4.4)

[Source: Reviewer.]
The classification of infections is based on medical terminology used in MedDRA v19.0.
[a]: Some subjects may have more than one infections. Counts (Percentages) are presented.
[b]: Rates are in events per 100 person-years.
Abbreviations: PBO=placebo; Q1=25th quantile; Q3=75th quantile; SD=standard deviation; TCZ=tocilizumab.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

I investigated the treatment effect of the TCZ arms relative to the placebo arms by the following key demographic subgroups, namely, gender (male or female), age groups (< 65 years vs ≥ 65 years), and geographical region (US vs non US). Efficacy subgroup results by race or ethnicity were not conducted since 97.2% of the patients were white, and 96% of the patients were neither Hispanic nor Latino. Additional subgroups analyses of clinical relevance were included: relapse vs new onset patients, body weight ≥ 60 kg vs body weight < 60 kg, and BMI < 25 kg/m^2 vs BMI ≥ 25 kg/m^2. In addition, a BMI subgroup defined by categories BMI < 22 kg/m^2 vs 22 kg/m^2 ≤ BMI ≤ 28 kg/m^2 vs BMI > 28 kg/m^2 was also investigated. All results presented are exploratory and are not controlled for multiplicity.

Difference in proportions for each dose as compared to the placebo arm with 26-week prednisone taper and the placebo arm with 52-week prednisone taper were estimated for each subgroup of interest. I included 95% unadjusted confidence intervals based on the unpooled estimate of the proportions for each treatment group within the subgroup. No p-values were provided in any of these analyses. Given the limited sample size of the subgroups, the confidence intervals tend to be considerably wider than for the overall study population.

Subgroup analyses results are presented for the primary composite endpoint of sustained remission and for the individual component of sustained absence of GCA signs and symptoms in Figure 5 and Figure 6 respectively. The estimated treatment effects based on the applicant's defined primary endpoint of sustained remission were consistently in the direction favoring the efficacy of both tocilizumab arms relative to both the placebo with 26-week prednisone taper arm and the placebo with 52-week prednisone taper arm across the subgroups.

In the analyses of sustained remission using absence of signs and symptoms of GCA alone, the estimated treatment effects across the various subgroups evaluated were attenuated towards the null hypothesis of no difference but still consistently trended in favor of TCZ QW relative to both placebo arms. The estimated subgroup treatment effects comparing TCZ Q2W relative to

both placebo arms was also generally consistent in the direction of benefit, but tended to be smaller than the estimated effects for the QW TCZ dose.

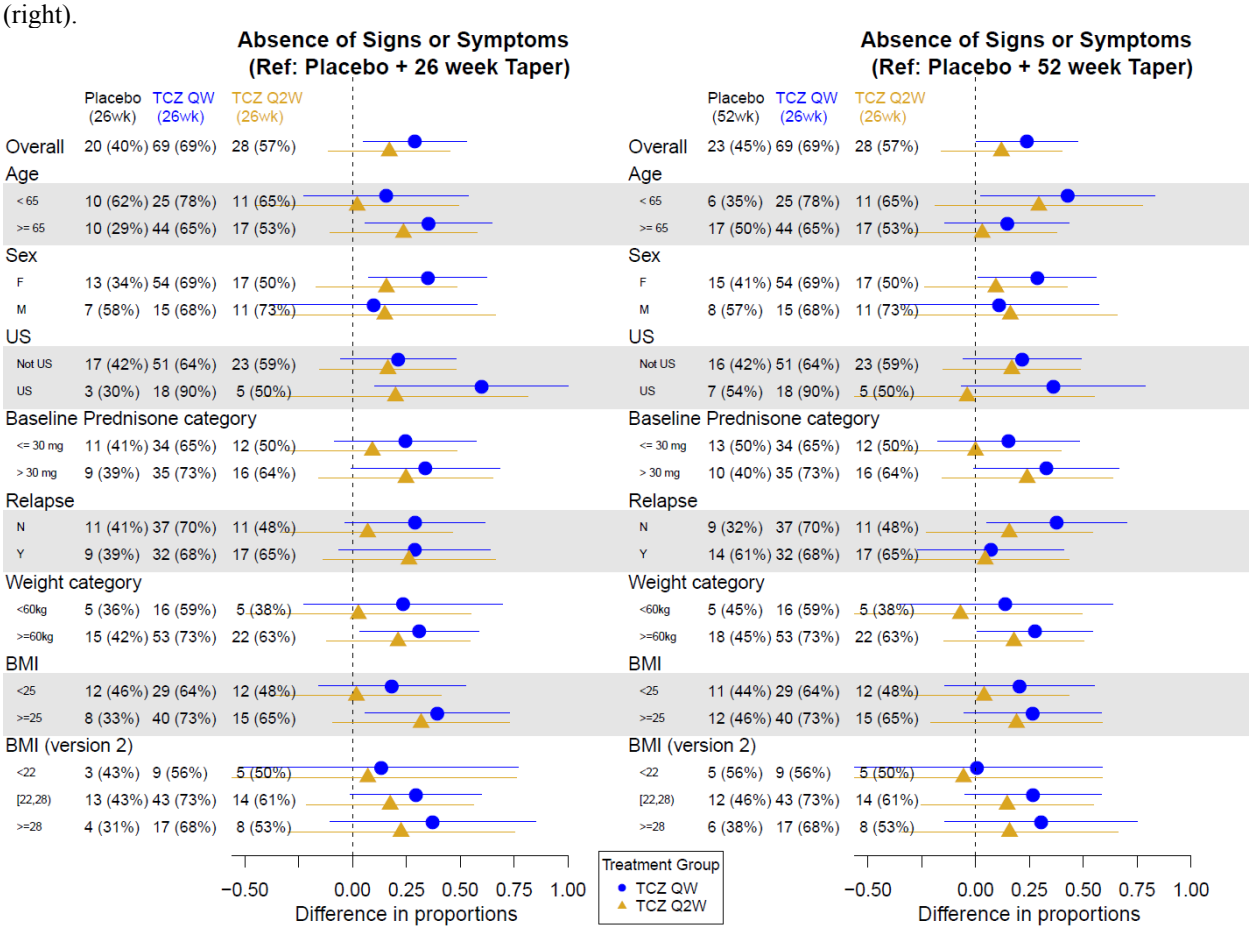
Figure 5 Forest plot of the subgroup analysis results for the applicant's defined sustained remission endpoint based on comparisons with placebo with 26-week taper (left) and placebo with 52-week taper (right).

[Source: Reviewer created the figure.]

Counts (percentages) were provided as descriptive statistics. 95% CI limits based on unpooled variance were used.

Abbreviations: BMI=body mass index denoted by weight (kg) divided by square of height (m); CI=confidence interval; N=no; PBO=placebo; QW=every week; Q1=25th quantile; Q2W=every other week; Q3=75th quantile; Ref=reference; SD=standard deviation; TCZ=tocilizumab; WK=week; Y=yes.

Figure 6 Forest plot of the subgroup analysis results for the individual component sustained absence of signs or symptoms of GCA based on comparisons with placebo with 26-week taper (left) and placebo with 52-week taper (right).



[Source: Reviewer created the figure.]
Counts (percentages) were provided as descriptive statistics. 95% CI limits based on unpooled variance were used.
Abbreviations: BMI=body mass index denoted by weight (kg) divided by square of height (m); CI=confidence interval; N=no; PBO=placebo; QW=every week; Q1=25th quantile; Q2W=every other week; Q3=75th quantile; Ref=reference; SD=standard deviation; TCZ=tocilizumab; WK=week; Y=yes.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In summary, there were various statistical issues identified that were important to evaluating the efficacy of tocilizumab and the reliability of the applicant's data.

- Comparison with under treated control

In this review, we focus on the superiority evaluation against placebo with 52-week prednisone taper for the following reasons. As reiterated in various meeting correspondences with the applicant, the placebo arm with 26-week prednisone taper is considered to involve a more rapid taper than what is typically done in standard of care clinical practice. Some patients may require

a more cautious tapering schedule than other patients, and patients unable to adapt to the rapid tapering schedule would be more likely to have a disease-related flare. Given these concerns, the tocilizumab arms could demonstrate superiority to an under treated placebo arm with 26-week taper while not improving signs and symptoms of GCA relative to the slower 52-week taper that is more representative of standard of care.

The proposed non-inferiority comparison with 52-week prednisone taper also did not address the Agency's concerns; the applicant did not adequately justify why ruling out a loss of efficacy as large as the proposed NI margin should be considered clinically meaningful and sufficient for approval. Furthermore, the presence of a placebo arm with the more appropriate 52-week taper allows a direct comparison to evaluate the efficacy of tocilizumab. Hence, this review focused on the evaluation of superiority over the placebo arm with 52-week steroid taper.

This determination was based on the scientific and clinical considerations, the Agency's prior correspondences with the applicant, as well as the scientific goal of WA28119 to determine the effectiveness of TCZ with an appropriate steroid taper (e.g., 26 weeks) relative to current standard of care. Based on the primary endpoint of protocol-defined sustained remission, both dosing regimens of TCZ demonstrated convincing superiority over the placebo arm with 52-week prednisone taper, supporting the effectiveness of tocilizumab for treating GCA.

- Limitations of composite endpoint

The proposed primary efficacy endpoint of sustained remission at Week 52 following induction of remission at Week 12 is a composite endpoint. This primary endpoint evaluates not only patient disease symptoms but also additional components such as acute phase reactants and the ability of the patient to adhere to the steroid taper without flaring. Thus, it is unclear whether a treatment effect in the primary efficacy analysis could be driven by tocilizumab's known effects on the inflammatory biomarkers CRP and ESR without tocilizumab having any effect on the direct signs and symptoms of the patient's disease. Various sensitivity analyses proposed by the applicant were considered inadequate because these analyses could still be driven by other components of the composite endpoint such as acute phase reactants or successful steroid tapering.

Thus, the additional supportive analyses based on the individual components are critical to determine whether there are symptomatic improvements in patients' disease when treated with TCZ. In these supportive analyses, both TCZ QW and TCZ Q2W showed consistent and compelling evidence for a higher probability of responses than the placebo arms based on acute phase reactants, consistent with the known properties of TCZ to lower acute phase reactants. Results based on successful prednisone taper regardless of acute phase reactants, signs and symptoms, and adherence to study treatment also showed trends of benefit for both TCZ QW and TCZ Q2W.

Of these individual component analyses, the most reliable and direct measure of how patients function and feel was considered the absence of signs and symptoms of GCA alone. In this critical analysis, the comparison of TCZ QW relative to the placebo arm with an appropriate taper demonstrated compelling (estimate 24%; 99.5% CI 0.3% to 46%) evidence of improvements in patient symptoms. The efficacy for TCZ Q2W was less compelling but demonstrated numerical improvements (estimate 12%; 99.5% CI 16% lower to 40% higher) in patient symptoms of GCA relative to the placebo arm with 52-week taper. There were trends

toward a dose response, i.e., greater improvement on TCZ QW than Q2W in analyses of absence of signs and symptoms of GCA alone.

Furthermore, patient-reported outcomes also showed numerical trends consistent with general improvement in how patients feel and function on TCZ.

- Missing data

The presence of missing data can affect the interpretation of the study results. Approximately 14% of the subjects were not followed through Week 52 and there were differentially higher discontinuation rates related to adverse events on the TCZ arms relative to the placebo arms. I defer the reader to the medical reviewer summary on whether there were any unanticipated or concerning adverse events associated with the use of TCZ.

Tipping point sensitivity analyses provided reassurance of the robustness of the applicant's results to violations in assumptions about the missing data.

- Total steroid use

The analysis of cumulative prednisone dose by the applicant presents challenges in interpretation when patients discontinued from the study prior to Week 52. The analysis assumption that subjects who withdraw from the study do not receive any additional steroid dosing is highly implausible. It is challenging to reliably estimate how much steroids might be used after discontinuation because there are differences in clinical practice in terms of steroid tapering and due to the possibility that patients who drop out may be systematically different than patients who remain in the study. Despite these limitations, in additional analyses of total prednisone use standardized to follow-up in the study, both TCZ QW and TCZ Q2W showed considerably lower total prednisone use relative to the placebo arms, providing additional supportive evidence of benefit.

- Time to first flare following GCA remission

This analysis conditions on a post-randomization variable (whether a patient achieved remission), such that differences between the arms (or lack thereof) could be due to treatment effects or could be due to differences in the patient characteristics of the subsets who achieved remission on the different arms. The analysis does not preserve the integrity of randomization [redacted] (b) (4) An appropriate design to address this question would include randomization to different treatment arms after patients achieve remission on tocilizumab.

- Single pivotal study

The FDA Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* indicates situations in which a single study of a new treatment may be combined with independent substantiation from related, supportive study data to provide evidence of effectiveness. In particular, the Guidance notes that supportive data may come from studies of a different dose or studies in a slightly different patient population, depending on the quality and outcomes of such related studies.

Tocilizumab has been found to be safe and effective and has been approved in multiple different rheumatologic disease populations (rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis). The applicant conducted the single pivotal,

multi-center study WA28119 to provide evidence of TCZ QW as a treatment for GCA while further investigating the Q2W dosing. The applicant chose to control the overall Type 1 error rate at the 2-sided level of 1%, adjusted for multiplicity by further testing the primary endpoint for each dose at 2-sided level of 0.005; this significance level is more stringent than the typical two-sided 5% level. Furthermore, the analysis of the primary endpoint of sustained remission comparing the TCZ QW arm placebo with 52-week taper demonstrated a large and highly statistically significant effect (estimated difference: 38%; $p<0.0001$).

Results were shown to be robust to alternative missing data assumptions in sensitivity analyses investigating plausible scenarios, and further showed benefit in analyses of each of the individual components of this composite endpoint. The most critical supportive analysis based solely on absence of signs and symptoms of GCA regardless of inflammatory markers, prednisone taper, and study drug adherence showed a more than 20% improvement on TCZ QW as compared to placebo with 52-week taper, with strong evidence against the null hypothesis of no effect ($p=0.0046$). In addition, descriptive analyses also suggested that the total cumulative prednisone use adjusted for study follow-up on TCZ QW tended to be roughly half that of patients on the placebo arms, and there were numerical trends of improvement in patient-reported outcomes. The totality of evidence therefore demonstrated the efficacy of TCZ QW with an appropriate steroid taper in treating GCA despite the reliance on a single study.

- Dose selection

This study investigated QW and Q2W dosing of TCZ with a 26-week prednisone taper and showed compelling results based on the protocol-defined primary endpoint for both doses. In the critical supportive analysis based on signs and symptoms of GCA alone, results remained convincing for the higher QW dose. However, there was not statistical evidence of an effect for the Q2W dose with 26-week prednisone taper in this supportive analysis, and although there remained numerical trends toward benefit, estimates suggested a dose-response relationship favoring the higher QW dose. Furthermore, a numerically higher proportion of patients required additional escape prednisone and a higher cumulative prednisone dose adjusted for study follow-up were observed for the Q2W dosing relative to the TCZ QW dosing. One question of interest that remains is whether the Q2W dosing might be more appropriately paired with a different, slower steroid taper than the QW dosing.

Despite the somewhat less convincing evidence of efficacy for the TCZ Q2W, discussions with the clinical team have suggested that it may useful to have both doses included in labeling. For example, it may be useful to have the flexibility of using TCZ Q2W as an alternative for patients who cannot tolerate the more frequent QW dosing regimen of TCZ (noting that there were higher discontinuation rates on this arm than other arms in this phase 3 study).

Furthermore, it is unclear whether tocilizumab QW should be used chronically in GCA patients who achieve remission, or whether withdrawal or down-titration to a dose such as Q2W might be reasonable in such patients. The phase 3 study was not designed to address this. To answer such a question reliably, the most appropriate approach would be to perform a post-marketing randomized withdrawal study, for example, a study where patients who achieve remission on TCZ QW are randomized to either continue on the TCZ QW regimen, step down to the TCZ Q2W regimen, or withdraw to placebo.

5.2 Collective Evidence

Evidence from the evaluation of the primary endpoint of sustained remission from week 12 to week 52 supports the effectiveness of the QW dose of tocilizumab for treatment of GCA. Compelling evidence was also observed for TCZ QW with 26-week prednisone taper in various supportive analyses based on individual components of the endpoint, such as GCA signs and symptoms alone, against the relevant standard of care control arm, i.e., the placebo arm with the 52-week prednisone taper. Additional missing data sensitivity analysis supported the finding of effectiveness for TCZ QW with 26-week prednisone taper. There was also a markedly lower amount of total prednisone used in the TCZ arms relative to any of the placebo groups, a finding which is of clinical interest due to the side effects of steroids. Finally, results for patient-reported outcomes endpoints trended towards a benefit for TCZ QW with 26-week prednisone taper.

There was also statistical evidence for the efficacy of TCZ Q2W with 26-week prednisone taper versus placebo with 52-week taper based on the protocol-defined sustained remission primary endpoint. However, results were less convincing in the key supportive analysis of the absence of signs and symptoms of GCA alone from Week 12 through Week 52, with numerical trends suggesting less benefit than with the applicant's proposed QW dosing with 26-week prednisone taper.

In summary, there is substantial and compelling evidence from this single pivotal study supporting the effectiveness of TCZ QW in combination with an appropriate steroid taper (expected to be shorter than in current standard of care) for treatment of GCA. There is some evidence for the Q2W with 26-week prednisone taper, but it is less persuasive than the evidence for the higher dose with 26-week prednisone taper.

5.3 Conclusions and Recommendations

The applicant has provided results from a pivotal, phase 3, multi-arm, double-blind, placebo-controlled study, WA28119, to support the safety and effectiveness of tocilizumab for the treatment of adult patients with GCA. There is substantial and compelling evidence from this single pivotal study supporting the efficacy of TCZ QW and TCZ Q2W in combination with an appropriate steroid taper (e.g., over 26 weeks) as compared to placebo plus a similar steroid taper and placebo plus a slower steroid taper that is more representative of standard of care. Evidence for TCZ Q2W was less convincing than for the higher TCZ QW dose in key supportive analyses.

There are limitations to study WA28119. Recognizing the clinical importance of minimizing steroid use, it is of interest to understand the extent to which the use of TCZ can minimize steroid use while maintaining its effectiveness, i.e., to understand what is the most appropriate steroid tapering strategy to use when initiating TCZ in GCA. It is also of clinical interest to understand whether patients can remain free of GCA-related signs and symptoms once they enter remission, and if such patients should continue to take TCZ at the same or perhaps a lower dose, or should withdraw from treatment. Study WA28119 was not designed to answer these questions, which are of public health importance. Therefore, additional study (ies) would be helpful to inform appropriate use of tozilizumab in treating GCA.

Nonetheless, this single pivotal study has provided statistically significant and robust results, and adequately met the primary and key secondary objectives in demonstrating the efficacy of the proposed TCZ QW dosing in treatment of adult patients with GCA.

5.4 Labeling Recommendations

1. The primary endpoint of sustained remission should be clearly defined in the CLINICAL STUDIES section. The definition also should (b) (4)
2. (b) (4)
3. I recommend including components of sustained remission from Week 12 through Week 52, i.e., absence of signs and symptoms of GCA, absence of ESR $\geq$ 30mm/hr that is attributable to GCA, absence of successive elevated CRP > 1mg/dL, and successful prednisone taper with less than 100mg use from Week 12 through Week 52 to allow practicing clinicians a full picture of how the individual components are affected by TCZ. A 99.5% CI based on the pooled variance may be included.
4. (b) (4)
5. (b) (4)
6. The cumulative prednisone dose results are considered important to provide clinicians some description of the amount of prednisone taken during the study. We recommend descriptive statistics adjusting for follow-up time, as well as reporting of the number of subjects who did not complete the study through Week 52.
7. Summary results for infection rates should include results for TCZ Q2W. The total study follow-up and number of infections should be considered for inclusion as well.

6 APPENDICES

6.1 Additional results

Table 19 Sensitivity analyses conducted by the applicant for primary endpoint of sustained remission excluding individual components of the composite endpoint.

	PBO QW + 26-week Prednisone Taper (N=50)	PBO QW + 52-week Prednisone Taper (N=51)	TCZ QW + 26-week Prednisone Taper (N=100)	TCZ Q2W + 26-week Prednisone Taper (N=49)
Sustained remission excluding elevated ESR attributable to GCA	10 (20%)	17 (33%)	59 (59%)	27 (55%)
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			39% (15%, 63%)	35% (8%, 62%)
p-value			<0.0001	0.0004
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			26% (2%, 50%)	22% (-6%, 50%)
p-value			0.0030	0.029
Sustained remission excluding successful prednisone taper	7 (14%)	9 (18%)	59 (59%)	26 (53%)
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			45% (21%, 69%)	39% (12%, 66%)
p-value			<0.0001	<0.0001
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			41% (17, 65)	35% (9%, 62%)
p-value			<0.0001	0.0002
Sustained remission (excluding normalization of CRP and successful prednisone taper)	14 (28%)	14 (27%)	67 (67%)	27 (55%)
Vs PBO + 26-week taper				
Difference in proportions (99.5% CI)			39% (15%, 63%)	27% (-1%, 55%)
p-value			<0.0001	0.0075
Vs PBO + 52-week taper				
Difference in proportions (99.5% CI)			40% (15%, 64%)	28% (0%, 55%)
p-value			<0.0001	0.005

[Source: Reviewer created above table using STATA 14.0.]

[a] : Reviewer results differ from the applicant's due to (1) P-values were obtained based on the Cochran-Mantel-Haenszel stratified adjustment for imputed baseline prednisone category; (2) Reviewer accounted for an additional subject lost to follow-up who should have been considered a non-responder in applicant analyses.

Abbreviations: CI=confidence interval; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; GCA=giant cell arteritis; PBO=placebo; QW=every week; Q2W=every other week; TCZ=tocilizumab.

6.2 References

1. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, et al., 2007, Infliximab for Maintenance of glucocorticosteroid-Induced Remission of giant cell arteritis: A Randomized Trial, Ann Intern Med, 146:621-630.

2. Kronmal, R, 1993, Spurious Correlation and the Fallacy of the Ratio Standard Revisited, Journal of the Royal Statistical Society, Series A (Statistics in Society), 156(3), 379-392.

3. Salvarani, C., Pipitone N., Versari, A., Hunder G., 2012, Clinical features of polymyalgia rheumatic and giant cell arteritis, Nat. Rev. Rheumatol. 8, 509–521.
4. Yan X, Lee S, Li N, 2009, Missing data handling methods in medical device clinical trials, J Biopharmaceutical Statistics, Nov, 19(6):1085- 1098.

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/s/

WILLIAM J KOH
04/25/2017

GREGORY P LEVIN
04/25/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF A BLA

BLA #:	125472/125276
Supplement #:	024/112
Related IND #:	113654
Product Name:	Actemra® (Tocilizumab) 162mg every week (QW) subcutaneous injection
Indication(s):	Treatment of Adult Patients with Giant Cell Arteritis
Applicant:	Roche/Genentech
Dates:	Received 22nd Nov 2016
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	William Koh, PhD, Statistical Reviewer
Concurring Reviewers:	Gregory Levin, PhD, Statistical Team Leader
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Rachel Glaser, MD Medical Reviewer Nikolay Nikolov, MD, Medical Team Leader
Project Manager:	Nina Ton

1. Introduction

The applicant has submitted the results of a single pivotal Phase 3 study (WA28119) to support the safety and effectiveness of Actemra® (tocilizumab) with the proposed dosing of 162mg administered subcutaneously once every week, in combination with a tapering course of glucocorticoids for treatment of adult patients with Giant Cell Arteritis. The sponsor also proposed that TCZ could be used alone following discontinuation of glucocorticoids. This BLA supplement is given a given a Priority Review Designation for Giant Cell Arteritis.

1.1 Placebo controlled study WA28119

Study WA28119 was a randomized, double-blind, multi-site, multiple arm, parallel group, placebo-controlled study conducted to assess the efficacy and safety of tocilizumab (Actemra®), denoted as TCZ for the rest of this review, among adult patients with Giant Cell Arteritis (GCA).

Randomization: The study screened 363 patients, of which 251 patients who met eligibility criteria were randomized into the following treatment arms in a 1:1:1:2 ratio: placebo in combination with 26-week prednisone taper (n=50), placebo in combination with 52-week prednisone taper (n=51), TCZ every 2 weeks (Q2W) in combination with 26-week prednisone taper (n=50*), and TCZ every week (QW) in combination with 26-week prednisone taper

(n=100). Randomization was stratified by baseline use of prednisone dose dichotomized by either ≤30 mg/day or > 30mg/day. *One randomized subject from the TCZ Q2W in combination with 26 week prednisone taper arm withdrew from the study prior to receiving any treatment. Thus, based on protocol definition of intent-to-treat (ITT) of at least 1 dose, only 49 patients from TCZ Q2W with 26-week prednisone taper were included in the ITT analysis.

Blinding is an important aspect in this trial. TCZ is known to suppress CRP levels and thus it is vital that physicians treating the patients are blinded from such knowledge. In this study, a dual assessor approach is employed to maintain this blind. An Efficacy Assessor would be a rheumatologist responsible to assess the clinical signs and symptoms of GCA (without CRP and ESR), assessment of adherence to protocol defined prednisone taper regimen, recording of adverse events during double blind period of 52 weeks (Part 1). An independent Safety assessor, who cannot be the Efficacy Assessor, would have access to only the patient's laboratory data. In addition, the protocol states that it is "*mandatory and essential that assessments by the Efficacy Assessor be completed before assessments by Safety Assessor*".

Visit schedule: Patients were assessed weekly for the first four weeks of the study, following which visit schedules were conducted every 4 weeks from Week 4 to Week 52.

The study design consisted of two distinct periods: a 52-week double blind period after randomization and a further 104-week open-label extension following the end of the 52-week double-blind period. Figure 1 presents the key features of the study design.

Key primary objective and respective endpoint: The primary objective of study WA28119 was to determine whether TCZ compared to placebo, in combination with a 26-week prednisone taper regimen was efficacious as a treatment for adult patients in GCA.

This primary endpoint is assessed by the proportion of patients who satisfy the protocol-defined definition of sustained remission at 52 week. These patients must have 1) attained GCA remission by week 12 (induction of remission), and 2) have sustained continuous GCA remission between week 12 to week 52 (sustained remission), and 3) adhere to the protocol-defined prednisone taper regimen (must be less than 100mg of corticosteroids (CS) from Week 12 onwards).

A GCA remission is (a) the absence of a flare assessed by an investigator and (b) normalization of C-reactive protein (CRP < 1mg/dL). A flare is the recurrence of signs or symptoms of GCA and/or an erythrocyte sedimentation rate (ESR) ≥ 30mm/h attributable to GCA. Non normalization of CRP is defined such that CRP is elevated on two consecutive visits or that CRP is elevated at a visit and missing at the next consecutive visit.

Key secondary objectives and respective endpoints: A key secondary objective was a non-inferiority comparison to determine whether TCZ in combination with 26-week prednisone taper regimen was non-inferior over placebo in combination with 52-week prednisone taper regimen. The same endpoint of sustained remission was used to assess this key secondary objective.

Exploratory secondary objectives of the study included determining whether doses of TCZ in combination with 26-week prednisone taper regimen was efficacious over placebo groups based on (A) time to GCA disease flare after clinical remission, (B) cumulative CS dose over

52 weeks, (C) patient global assessment of disease activity on a visual analogue scale (VAS) of 0 – 100mm, and (D) change from baseline in SF-36 health survey at Week 52.

Statistical Significance/Multiplicity adjustment: All statistical tests were conducted using a 2-sided alpha level of 1%. For the key secondary objective, a 99.5% CI will be used to assess the non-inferiority comparison between TCZ with 26-week prednisone taper vs placebo with 52-week prednisone taper. The lower bound of the two sided 99.5% CI of ≥ -22.5% (M2) would "demonstrate non inferiority" to placebo with a 52-week prednisone tapering while "allowing for preservation of at least 50% of a minimum treatment effect of pre-specified treatment effect of 45% (M_1) observed with corticosteroid therapy alone".

A multiplicity adjustment is performed by testing two hierarchies each using an alpha of 0.5% in the fixed sequence within each hierarchy.

Hierarchy 1 will first test the superiority of TCZ QW with 26-week CS taper vs placebo with 26-week CS taper, followed by the non-inferiority of TCZ QW with 26-week CS taper vs placebo with 52-week CS taper.

Hierarchy 2 will first test the superiority of TCZ Q2W with 26-week CS taper vs placebo with 26-week CS taper, followed by the non-inferiority of TCZ Q2W with 26-week CS taper vs placebo with 52-week CS taper.

Key aspects of the study design and the primary and secondary results were summarized in Table 1 by the reviewer based on sponsor's submitted materials.

Operational aspects: The first randomized screened patient was performed on July 22nd 2013. The last screened patient was randomized on April 21st 2015. Data cutoff for data analysis was made on April 11th 2016. No interim analysis was planned. An independent Data Monitoring Committee (iDMC) was convened to regularly review safety data at least twice a year. The iDMC charter was provided in the applicant's submission.

Figure 1 Study Design

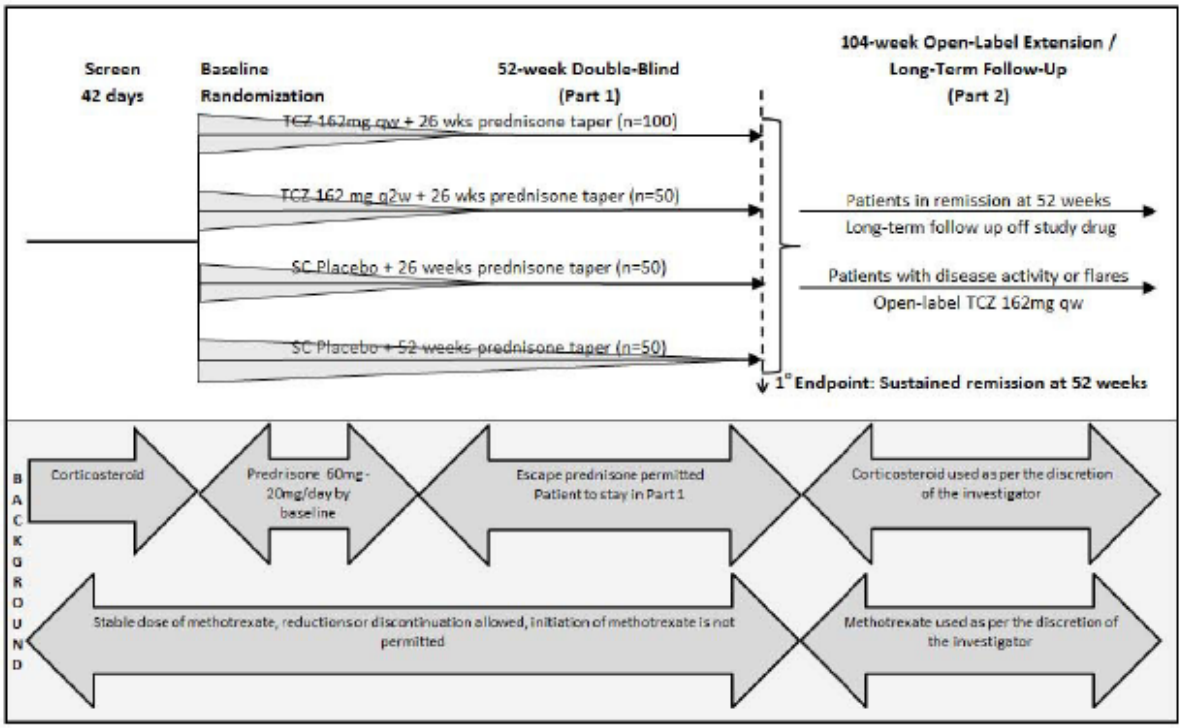

Figure 1 [Source: Study design for WA28119 obtained from sponsor's clinical study report section.]

Table 1: Summary of the Phase 3 study submitted by the sponsor.

Trial ID	Design^	Population	Treatment/ Sample Size	Endpoint/Analysis
WA28119	MC, R, DB, PG, PC; Part 1 DB for 52 wks; Part 2 OL for 104wks	New onset of GCA (within 6 weeks of baseline) OR Relapsing GCA patients (diagnosed > 6 weeks before baseline visit and prior treatment with ≥40mg/day prednisone for at least 2 weeks	1) TCZ 162mg qw + 26w taper (n=100) 2) TCZ 162mg q2w + 26w taper (n=49) 3) Placebo + 26w taper (n=50) 4) Placebo + 52w taper (n=51)	**Primary**[a] Proportion in sustained remission at 52w comparing 1 vs 3; Proportion in sustained remission at 52w comparing 2 vs 3; **Key Secondary**[b] Proportion in sustained remission at 52w comparing 1 vs 4; Proportion in sustained remission at 52w comparing 2 vs 4;

Source: Reviewer created the table based on sponsor submitted materials.
MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled, OL: Open-label extension
^: See Figure 1
[a]: Analysis was conducted by comparing the difference in proportions with an unadjusted 99.5% CI based on overall variance assumption (superiority comparison) and p-value obtained from a Cochran-Mantel-Haenszel test stratified by baseline prednisone usage.
[b]: Analysis was conducted by comparing the difference in proportions with an unadjusted 99.5% CI based on unequal variance assumption (non-inferiority comparison) and p-value obtained from an extended Mantel-Haenszel test based on normal approximation stratified by baseline prednisone usage.

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol and the Study Report

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Prior correspondence between the agency and the sponsor were made regarding the tapering strategy that may bias the trial in favor of the proposed treatment among patients in this disease. The sponsor has addressed the agency's concern by including an arm with a more appropriate tapering schedule. Appropriate blinding strategy is used to prevent knowledge of acute phase reactants that may unblind the patient from the treatment arm.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Primary and secondary endpoints were specified in the protocol and statistical analysis plans. Statistical methods for all key primary, key secondary and, secondary analyses were also provided in version 2 of the sponsor's submitted SAP. Exploratory endpoints were described in the protocol and SAP.
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	There was no planned interim analysis made for the efficacy endpoint. DSMB monitoring is performed at approximately every 6 months to monitor the safety. Efficacy data is only provided to the DSMB upon request. A DSMB charter is provided by the sponsor. *An IR will be submitted to request for the agenda as well as the closed and open session minutes of these meetings.*
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	SAS codes are not provided by the sponsor. Statistical analysis plan cited reference for the tipping point analysis. Specific details on the choice of standard errors used to construct 95% CI were not documented in the SAP. The choice of CIs were different for the key primary and key secondary objectives.
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Sensitivity analyses based on agency's recommendations were also provided. In addition, a two-dimensional tipping point sensitivity analyses was also provided for the efficacy endpoints for sustained remission.

3. Electronic Data Assessment

Table 3 Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\cdsesub1\evsprod\BLA125472\0116\m5\datasets
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	Both SDTM and ADaM are provided
Are the define files sufficiently detailed?	define.pdf files are provided for both SDTM and ADaM datasets.
List the dataset(s) that contains the primary endpoint(s)	abase.xpt contains the primary endpoint of sustained remission coded by variable SREMTRFL. The dataset also contained the additional endpoints based on sustained remission with prednisone taper adherence (RSPANTFL) and (Sustained remission without taper adherence), PTAPADFL (prednisone taper adherence flag).
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	**The analysis datasets are sufficiently structured to allow analysis directly for the primary endpoint of interest.** The reviewers guide facilitated easy finding of the relevant files for the primary endpoint. Although documentation was provided on how the primary endpoint SREMTRFL was obtained from the individual sdtm files or which sdtm file to use, source code was not provided. The complexity of the computation may necessitate an IR for the individual text files used to construct the primary endpoint variable SREMTRFL.
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	To be discussed internally with the clinical team. Currently in progress.
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Only 1 pivotal study was conducted and submitted for this rare disease.

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

An IR for the following items was made on Dec14 2016 to request or clarify the following questions.

a) Submit safety results by sex, race, and age subgroups or clarify where such results are included in the submission.

b) Clarify the statistical methods, and provide programming code used to produce the subgroup analysis results presented in section 3.2.4 of the Summary of Clinical Efficacy.

c) Provide individual text files or executable copies of all programs and macros used to carry out the primary and secondary efficacy endpoint analyses as well as the sensitivity analyses.

d) Provide the original protocol and all amendments in an individual pdf file.

e) Provide the original statistical analysis plan and all amendments in another individual pdf file.

As of Dec 26 2016, the sponsor has provided sufficient materials required to file the current supplement.

Table 4 Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	X			The clinical study report is a massive document (>6000 pages) that comprises of 4 main sections: Core report, Primary data listings, study documentation, and bioanalytical reports. An IR was made to ask the sponsor to include all protocols, any additional revisions to the SAP in a separate file.
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).	X			Additional sensitivity analyses requested by the agency were briefly described in the reviewers-guide.pdf under section 5 within datasets but not mentioned in the protocol.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	X			An information request was made on Dec 14th 2016 to request for the investigation of safety by subgroups. The sponsor provided the information on Dec 23rd 2016.
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			Selected SDTM data (FA.xpt, DM.xpt) were briefly cross-checked with key components in the GCA diagnosis and demographics section of the acrf.pdf to ensure correct components were captured in the sdtm dataset. No documentation was provided on how the key primary endpoint was derived from the sdtm files. An IR may be required for SAS files to verify constructing the key primary endpoint variable.

Content Parameter	Yes	No	NA	Comments
Application appears to be free from any other deficiency that renders the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	X			Key macros and programs for the efficacy and sensitivity analyses were submitted on Dec 23rd 2016 after an IR was made on the 14th Dec 2016.

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

YES.

5. Comments to be conveyed to the Applicant

None.

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/s/

WILLIAM J KOH
01/24/2017

GREGORY P LEVIN
01/24/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s112

OTHER REVIEW(S)

Division of Pulmonary, Allergy, and Rheumatology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 125472/S-024 and BLA 125276/S-112

Name of Drug: Actemra (tocilizumab) SC and IV

Applicant: Genentech, Inc.

Labeling Reviewed

Submission Date: November 22 and 23, 2016

Receipt Date: November 22 and 23, 2016

Background and Summary Description: Roche submitted an efficacy supplement for a new indication of Giant Cell Arteritis (GCA) for Actemra SC on November 22, 2016. The applicant also submitted a labeling supplement dated November 23, 2016, for Actemra IV for the purpose of aligning the common prescribing information for the two routes of administration.

Review

A side-by-side comparison of the revised labeling submitted on November 22 and 23, 2016, to the last approved labeling for BLA 125472/S-018 dated September 23, 2016, was conducted.

Recommendations

There were no additional changes other than those proposed in the supplements submitted on November 22 and 23, 2016. I recommend approval of these supplements.

Please note the following reviews:

CDTL Memo by Nikolay Nikolov, MD, dated May 8, 2017
OPDP review by Adewale Adeleye, PharmD, MBA, dated May 1, 2017
Clin Pharm review by Manuela Grimstein, MSc, PhD, dated April 29, 2017
Clinical review by Rachel Glaser, MD, dated April 28, 2017
Patient labeling review by Twanda Scales, MSN/Ed., BSN, RN, dated April 28, 2017
DMEPA review by Teresa McMillan, PharmD, dated April 26, 2017
Statistical review by William Koh, PhD, dated April 25, 2017

Nina Ton	May 12, 2017
Regulatory Project Manager	Date
Ladan Jafari	May 12, 2017
Chief, Project Management Staff	Date

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/s/

PHUONG N TON
05/12/2017

LADAN JAFARI
05/12/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 1, 2017

To: Nina Ton, Pharm. D. Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm. D., MBA, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

Subject: BLA 125472 / S-024
BLA 125276 / S-112
ACTEMRA (tocilizumab) injection, for intravenous use
injection, for subcutaneous use (Actemra)

Reference is made to DPARP's consult request dated January 4, 2017, requesting review of the proposed Package Insert (PI) and Medication Guide (MG) for ACTEMRA (tocilizumab) injection for intravenous use, injection for subcutaneous use (Actemra).

OPDP has reviewed the proposed PI and MG entitled, "BLA 125472 S-024 Actemra SCPI.docx" that was available in SharePoint on April 28, 2017, at 11:54am. OPDP has no comments on the proposed labeling (see below).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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ADEWALE A ADELEYE
05/01/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 28, 2017
To:	Badrul Chowdhury, MD Director **Division of Pulmonary, Allergy, Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, MSN/Ed., BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Actemra (tocilizumab)
Dosage Form and Route:	Injection for Intravenous Infusion
Application Type/Number and Supplement Number:	BLA 125276 S-112 BLA 125472 S-024
Applicant:	Genentech, Inc. (Roche)

1 INTRODUCTION

On November 22, 2016, Roche submitted for the Agency's review a Biologic License Application (BLA) Efficacy Supplement for BLA 125472, ACTEMRA (tocilizumab) injection, for subcutaneous (SC) use. ACTEMRA (tocilizumab) injection for SC use was approved on October 21, 2013 for the treatment of adult patients with moderately to severe active Rheumatoid Arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Reference is made to Roche's Cross-Reference to BLA 125276, ACTEMRA (tocilizumab) injection for intravenous (IV) use, for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA), approved by FDA on January 8, 2010.

For the purpose of aligning the common prescribing information, for two routes of administration, reference is also made to the Supplemental BLA submitted on November 22, 2016 to BLA 125472 which provides data to support a proposed new indication for ACTEMRA for the treatment of adult patients with Giant Cell Arteritis (GCA).

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on January 4, 2017 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for ACTEMRA (tocilizumab).

2 MATERIAL REVIEWED

- Draft ACTEMRA (tocilizumab) injection for intravenous use, injection for subcutaneous use MG received on November 22, 2016 and November 23, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on April 25, 2017.
- Draft ACTEMRA (tocilizumab) injection for intravenous use, injection for subcutaneous use Prescribing Information (PI) received on November 22, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on April 25, 2017.

3 REVIEW METHODS

In our focused review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
04/28/2017

MARCIA B WILLIAMS
04/28/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 26, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125276/S-112 and BLA 125472/S-024
Product Name and Strength:	Actemra (tocilizumab) Injection Intravenous administration: 80 mg per 4 mL, 200 mg per 10 mL, 400 mg per 20 mL Subcutaneous administration: 162 mg/0.9 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genentech Roche
Submission Date:	November 22, 2016 and November 23, 2016
OSE RCM #:	2016-2809
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader (acting):	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the Prescribing Information (PI) for BLA 125276/S-112 and BLA 125472/S-024, Actemra (tocilizumab) Injection submitted on November 22, 2016 and November 23, 2016. The Applicant submitted an Efficacy Supplement which proposes a new indication for the treatment of adult patients with Giant Cell Arteritis (GCA). The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) requested that we review the proposed PI for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Genentech Roche is proposing a new indication for the treatment of adult patients with Giant Cell Arteritis (GCA). The proposed dose and frequency for GCA is 162 mg once weekly as a subcutaneous injection, in combination with a tapering course of glucocorticoids. The currently approved Actemra dosage forms and strengths support the proposed GCA dose and frequency.

In addition, the Prescribing Information adequately reflects the proposed GCA dose and frequency.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the proposed Prescribing Information acceptable from a medication error perspective and do not have any recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Actemra that Genentech Roche submitted on November 22, 2016.

Table 2. Relevant Product Information for Actemra	
Initial Approval Date	2010
Active Ingredient	Tocilizumab
Indication	Treatment of Adult Rheumatoid Arthritis (RA), Systemic Juvenile Idiopathic Arthritis (SJIA), and Polyarticular Juvenile Idiopathic Arthritis (PJIA)
Route of Administration	Intravenous and Subcutaneous
Dosage Form	Injection
Strength	80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL, 162 mg/0.9 mL
Dose and Frequency	**Rheumatoid Arthritis** ***Recommended Adult Intravenous (IV) 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 (SC) 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 **Polyarticular Juvenile Idiopathic Arthritis** ***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 **Systemic Juvenile Idiopathic Arthritis** ***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
How Supplied	• Supplied as a sterile concentrate, preservative-free

	single-use vial (20 mg/mL) solution for intravenous infusion. Supplied individually or in box of 4 single-use vials. • Supplied as a sterile preservative-free liquid solution in a single-use prefilled syringe
Storage	Refrigerated at 2˚C to 8˚ C (36˚ to 46˚ F). Do not freeze. Store in the original container to protected from light.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 6, 2017, we searched the L:drive and AIMS using the terms, Actemra and tocilizumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 20 previous reviews, and none of these reviews were relevant to this review.

APENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Actemra labels and labeling submitted by Genentech Roche on November 22, 2016.

- Prescribing Information

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
04/26/2017

SARAH K VEE
04/26/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s112

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PeRC Meeting Minutes
April 19, 2017

PeRC Members Attending:
John Alexander
Jacquline Yancy
Gettie Audain
Lily Mulugeta
Hari Cheryl Sachs
Kevin Krudys
Wiley Chambers
Gil Burkhart
Gerri Baer
Julia Pinto
Greg Reaman
Jinging Ye
Susan McCune
Megha Kaushal
Barbara Buch

Agenda

9:00	NDA 209195	Vosevi (Sofosbuvir/Velpatasvir/ Voxilaprevir) (Partial Waiver/Deferral) with Agreed iPSP	DAVP	Andrew Gentles	(b) (4)
					(b) (4)
10:25	NDA 21647	Vioxx (rofecoxib) Deferral Extension	DNP	Lana Chen	Migraine
10:35	NDA 202810	Oxtellar XR (oxcarbazepine) Deferral Extension	DNP	Stephanie Parncutt/ Heather Bullock	Adults: Adjunctive therapy in the treatment of partial seizures proposed indication: Adjunctive therapy in the treatment of partial seizures in children 6 to 17 years
10:45	BLA 125514/ S14	Keytruda (pembrolizumab) Partial Waiver/Deferral Plan (with no Agreed iPSP)	DOP 2	Sharon Sickafuse	(b) (4)
					(b) (4)

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[redacted] (b) (4)					
	sBLA 125472/ S24 & 125276/ S112	Actemra (Tocilizumab) Full Waiver with Agreed iPSP	DPARP	Nina Ton	Giant Cell Arteritis (GCA)

Sofosbuvir/Velpatasvir/Voxilaprevir (Partial Waiver/Deferral) with Agreed iPSP

- Proposed indication: [redacted] (b) (4)
- The PREA trigger is new active ingredient, dosing regimen, dosage form, route of administration, and indication with a PDUFA date of August 8, 2017.
- The division clarified that the deferral for 12 years and older because there will be a high level of treatment response. The division stated that the sponsor estimates enrolling 30 children into the deferred study. The deferral study report due date is April 2021.
- *PeRC Recommendations*:
  - The PeRC concurs with the division to grant a partial waiver from birth to less than <12 years of age because the product is directed to treatment failures and the existing direct-acting antivirals are expected to have extremely low rates of treatment failure for this age group.
  - The PeRC concurs with the division to grant a deferral in pediatric studies for ages 12 to 17 years of age as per the Agreed iPSP.

[redacted] (b) (4)

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(b) (4)

Vioxx (rofecoxib) Deferral Extension

- Proposed indication: Treatment of migraine
- The original approval of Vioxx was in 1999 for the treatment of osteoarthritis and for acute pain in adults. In March 2004, Vioxx was approved for use in the acute treatment of migraine in adults.
- Under PREA pediatrics studies were waived for ages 0-11, and deferred for ages 12-17, with a final report submission date of March 31, 2007. Merck voluntarily withdrew Vioxx from the market worldwide because of cardiovascular safety concerns with chronic use.
- The sponsor's 2013 request for deferral extension was granted with a final report due date of December 31, 2017.
- Vioxx is still not marketed in the U.S. (b) (4) The sponsor has requested a deferral extension from December 2017 until December 2021.
- The PeRC recommended that the PREA PMR should continue to exist if there is the possibility of this product returning to market. Although there was some discussion of whether there were alternatives to continued deferral extension (DE), the plan for DE appeared to be the best option.
- *PeRC Recommendations*:
    - The PeRC recommends that the PREA PMR remains in place and would not be removed unless the sponsor withdrew the NDA.
    - The PeRC agrees to a deferral extension
    - The PeRC agrees with the division in granting the deferral extension as outlined by the division, since Vioxx not being marketed in the US (delays due to safety issues).

Oxtellar XR (oxcarbazepine) Deferral Extension

- Proposed indication: Adjunctive therapy in the treatment of partial seizures in children 6 to 17 years
- The product was approved October 19, 2012. The sponsor has not submitted pediatric assessment for two PMRs deferred at initial approval until December 31, 2016.
- PREA PMRs include examination of PK and tolerability of an age appropriate extended release formulation for two age strata, children aged 1 month to 6 months as well as in patients 6 months to 4 years. These studies are to be followed by double blind efficacy and safety studies of oxcarbazepine ER for the treatment of partial onset seizures in the aforementioned age strata. The PREA PMRs issued are:

- **1938-4:** PK and tolerability in 1 mo to 6 mo with age appropriate formulation

Final Study Report: December 2016
New Final Study Report: January 2025

Reason for delay: Delayed due to difficulties in development of age appropriate formulation of oral liquid which failed (immediate release formulation).

- **1938-1:** Efficacy – safety <2 years , video EEG
  Final Study Report: September 2021
  New Study Report: November 2030

  Reason for delay: Must be preceded by 1983-4 which is delayed due to difficulty developing age appropriate formulation of the oral liquid which failed. (IR)

- **1938-2:** Efficacy 2-<6 yr, diary data
  Final Study Report: September 2021
  New Study Report: September 2031

  Reason for delay: COMPLETE dosing administration/palatability of placebo, (b) (4) for 6 mos to less than 6 years. (extended release formulation)

- **1938-3:** PK, tolerability 6 mo – 4 years, age appropriate formulation
  Final Study Report: December 2016
  New Study Report: September 2020 (Part 1)
  New Study Report: September 2024 (Part 2)

  Reason for delay: Need to complete study that demonstrates the (b) (4) may be delivered 1983-3 (part 1) before proceeding to PK, safety tolerability, 1983-3 (part 2)

- The division clarified that based on the recommendations from CMC they are denying the extension for all PMRs as the sponsor has not shown reasonable good faith attempts or efforts.
- The PeRC notes that the DE request seems excessive. Even if the sponsor was delayed for all of the roughly four years since approval, they are requesting an additional 9-10 years from the original requirements.
- *PeRC Recommendations*:
  - The PeRC concurs with the division's decision to deny the deferral extension request for all of the studies as the request does not seem reasonable as mentioned above.
  - PeRC notes that since efficacy and safety studies do not have a due date for final study report until 2021 then the sponsor will be listed as non-compliant for 2 PK studies and they should show good faith effort to start the PK trials.

Keytruda (pembrolizumab) Partial Waiver/Deferral Plan (with no Agreed iPSP)

- Proposed indication: (b) (4)

- The PREA trigger is new active ingredient and indication with a PDUFA date of March 28, 2017.
- The PeRC noted that there is no agreed upon iPSP for this BLA.
- The division clarified that a sponsor submitted an iPSP in August 30, 2016 which was withdrawn by the sponsor because they did not think they could complete the pediatric trial. The sponsor submitted a PSP later on as a plan to this BLA.
- The division stated that the disease is extremely rare and that they agree with the plan in the PSP and plan to accept the BLA. The division also clarified that they will most likely seek a Written Request in the future.
- *PeRC Recommendations*:
    - The PeRC concurs with the division to grant a partial waiver from birth to 6 months of age because the studies are highly rare impractical.
    - The PeRC concurs with the division to grant a deferral for pediatric studies for ages 6 months and older and an assessment in ages 12 to 17 years of age.

(b) (4)

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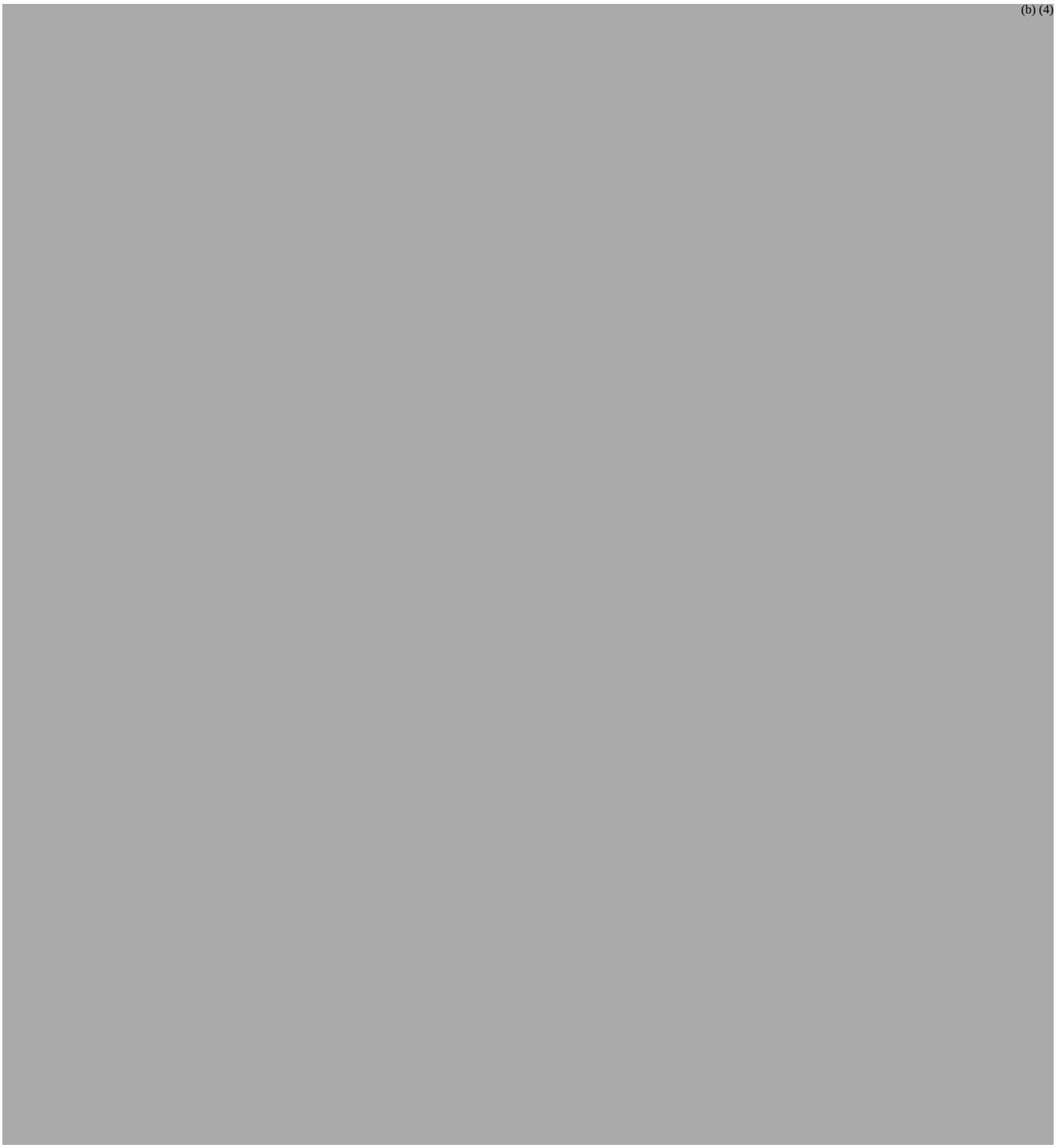

Actemra (Tocilizumab) Full Waiver with Agreed iPSP

- Proposed indication: Giant Cell Arteritis (GCA)
- *PeRC Recommendations*:
  - The PeRC agrees with the division to grant this full waiver as agreed upon in the iPSP.

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/s/

GETTIE AUDAIN
05/17/2017

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Hoffmann-La Roche Inc./Genentech, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 8, 2017

To: Karen Robertson Program Director, Regulatory	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: Hoffmann-La Roche Inc. c/o Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (650) 467-3198	**Fax number:** 301-796-9728
Phone number: (650) 737-2420	**Phone number:** 301-796-1648
Subject: BLA 125472/S-024 and BLA 125276/S-112 Actemra Labeling Comments #2	
Total no. of pages including cover and signature page 46	
Comments: Please acknowledge receipt and respond by May 10, 2017	

Document to be emailed to: robertson.karen@gene.com

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Hoffmann-La Roche Inc./Genentech, Inc.

Dear Ms. Robertson:

We are currently reviewing your supplemental BLAs submitted on November 22 and 23, 2016, and your proposed labeling submitted on May 2, 2017. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

In order to facilitate the review of your submission, provide the requested information no later than May 10, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your supplemental BLAs.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Hoffmann-La Roche Inc./Genentech, Inc.

Drafted by: NTon 5-8-2017
Cleared by: LJafari 5-8-2017
Finalized by: NTon 5-8-2017

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/s/

PHUONG N TON
05/08/2017

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Hoffmann-La Roche Inc./Genentech, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: April 25, 2017

To: Karen Robertson Program Director, Regulatory	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: Hoffmann-La Roche Inc. c/o Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (650) 467-3198	**Fax number:** 301-796-9728
Phone number: (650) 737-2420	**Phone number:** 301-796-1648
Subject: BLA 125472/S-024 and BLA 125276/S-112 Actemra Labeling Comments #1	
Total no. of pages including cover and signature page 53	
Comments: Please acknowledge receipt and respond by May 2, 2017	

Document to be emailed to: robertson.karen@gene.com

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Hoffmann-La Roche Inc./Genentech, Inc.

Dear Ms. Robertson:

We are currently reviewing your supplemental BLAs and your proposed labeling submitted on November 22, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

In order to facilitate the review of your submission, provide the requested information no later than May 2, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your supplemental BLAs.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Hoffmann-La Roche Inc./Genentech, Inc.

Drafted by: NTon 4-25-2017
Cleared by: LJafari 4-25-2017
Finalized by: NTon 4-25-2017

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/s/

PHUONG N TON
04/25/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-OPDP-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Nina Ton, Regulatory Project Manager, DPARP 301-796-1648

REQUEST DATE:	IND NO.	BLA NO	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
January 3, 2017		125472/S-024 125276/S-112	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Actemra (tocilizumab) SC and IV	Priority Review		April 21, 2017

NAME OF FIRM: Hoffmann–La Roche/Genentech, Inc.	PDUFA Date: May 22, 2017

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission: \\CDSESUB1\evsprod\BLA125472\0116

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: Genentech submitted two efficacy supplements dated November 22 and 23, 2016 for a new indication of Giant Cell Arteritis (GCA). DPARP respectfully requests OPDP to review the PI which includes the medication guide.

Filing/Planning Meeting: January 5, 2017
Mid-Cycle Meeting: February 16, 2017
Wrap-Up Meeting: April 25, 2017

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

PHUONG N TON
01/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Nina Ton, Regulatory Project Manager, DPARP
301-796-1648

DATE	IND NO.	BLA NO	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 3, 2017		125472/S-024 125276/S-112		November 22, 2016 November 23, 2016

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Actemra (tocilizumab) SC and IV	Priority Review		April 21, 2017

NAME OF FIRM: Hoffmann–La Roche/Genentech, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Genentech submitted two efficacy supplements dated November 22 and 23, 2016 for a new indication of Giant Cell Arteritis (GCA). DPARP respectfully requests OSE to review the PI which includes the medication guide.

Link to submission: \\CDSESUB1\evsprod\BLA125472\0116

Filing/Planning Meeting: January 5, 2017
Mid-Cycle Meeting: February 16, 2017
Wrap-Up Meeting: April 25, 2017

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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PHUONG N TON
01/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Nina Ton, Regulatory Project Manager, DPARP
301-796-1648

REQUEST DATE: January 3, 2017

BLA NO. 125472/S-024
125276/S-112

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Actemra (tocilizumab) SC and IV

PRIORITY CONSIDERATION:
Priority Review

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

April 21, 2017

SPONSOR: Hoffmann–La Roche/Genentech, Inc.

PDUFA Date: May 22, 2017

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\BLA125472\0116

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: Genentech submitted two efficacy supplements dated November 22 and 23, 2016 for a new indication of Giant Cell Arteritis (GCA). DPARP respectfully requests Patient Labeling Team to review the PI which includes the medication guide.

Filing/Planning Meeting: January 5, 2017
Mid-Cycle Meeting: February 16, 2017
Labeling Meetings: March 28 and April 6, 2017
Wrap-Up Meeting: April 25, 2017

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

PHUONG N TON
01/04/2017

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Genentech, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: January 4, 2017

To: Karen Robertson Program Director, Regulatory	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (650) 467-3198	**Fax number:** 301-796-9728
Phone number: (650) 737-2420	**Phone number:** 301-796-1648

Subject: BLA 125472/S-024 and 125276/S-112 Actemra Information Request

Total no. of pages including cover and signature page 3

Comments: Please acknowledge receipt and respond by January 11, 2017

Document to be emailed to: robertson.karen@gene.com

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Genentech, Inc.

Dear Ms. Robertson:

We are currently reviewing your submissions dated November 22 and 23, 2016, and have the following request for information.

Submit the following references cited on "Bioanalytical sample analysis report for study WA28119" file (validation reports of the bioanalytical PK method for study WA28119):

[4] Validation Report VR0688. B. Klunder, Validation of a high sensitive immunoassay method for the determination of Tocilizumab (TCZ) in human serum samples, 14 September 2010.

[5] Validation Report VR0892. M. Putman, Partial validation of the use of a vibrating shaker for the method for the determination of Tocilizumab in human serum samples, validation completed on 08 February 2011, reporting in progress.

[6] M. Bruins-Jager. High sensitive immunoassay method for the determination of Tocilizumab (TCZ) concentrations in human serum samples by ELISA, AI0688-8, 13 May 2013.

[7] M. Putman. High sensitive immunoassay method for the determination of Tocilizumab (TCZ) concentrations in human serum samples by ELISA, AI0688-9, 12 April 2016.

In order to facilitate the review of your submission, provide the requested information no later than January 11, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLAs.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Genentech, Inc.

Drafted by:	NTon 1-3-2017
Cleared by:	MGrimstein 1-3-2017
	AMarathe 1-3-2017
	LJafari 1-3-2017
Finalized by:	NTon 1-4-2017

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/s/

PHUONG N TON
01/04/2017

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Genentech, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: December 14, 2016

To: Karen Robertson Program Director, Regulatory	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (650) 467-3198	**Fax number:** 301-796-9728
Phone number: (650) 737-2420	**Phone number:** 301-796-1648
Subject: BLA 125472/S-024 and 125276/S-112 Actemra Information Request	
Total no. of pages including cover and signature page 3	
Comments: Please acknowledge receipt and respond by December 23, 2016	

Document to be emailed to: robertson.karen@gene.com

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Genentech, Inc.

Dear Ms. Robertson:

We are currently reviewing your submissions dated November 22 and 23, 2016, and have the following requests for information.

1. For Study WA28119:

    a. Submit safety results by sex, race, and age subgroups or clarify where such results are included in the submission.

    b. Clarify the statistical methods, and provide programming code used to produce the subgroup analysis results presented in section 3.2.4 of the Summary of Clinical Efficacy.

    c. Provide individual text files or executable copies of all programs and macros used to carry out the primary and secondary efficacy endpoint analyses as well as the sensitivity analyses.

    d. Provide the original protocol and all amendments in an individual pdf file.

    e. Provide the original statistical analysis plan and all amendments in another individual pdf file.

In order to facilitate the review of your submission, provide the requested information no later than December 23, 2016. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLAs.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125472/S-024
BLA 125276/S-112
Actemra (tocilizumab)
Genentech, Inc.

Drafted by:	NTon 12-14-2016
Cleared by:	LJafari 12-14-2016
	WKoh 12-14-2016
	GLevin 12-14-2016
Finalized by:	NTon 12-14-2016

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/s/

PHUONG N TON
12/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125472/S-024
BLA 125276/S-112

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

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

Attention: Karen Robertson
Program Director, Regulatory

Dear Ms. Robertson:

We have received your Supplemental Biologics License Applications (sBLAs) submitted under section 351(a) of the Public Health Service Act for the following:

BLA NUMBER:	125472 125276
SUPPLEMENT NUMBER:	S-024 S-112
PRODUCT NAME:	Actemra (tocilizumab) Injection for subcutaneous use, 162 mg/0.9 mL Actemra (tocilizumab) Injection for intravenous use, 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL
DATE OF SUBMISSION:	November 22, 2016 November 23, 2016
DATE OF RECEIPT:	November 22, 2016 November 23, 2016

These supplemental applications propose a new indication for Actemra for the treatment of adult patients with Giant Cell Arteritis (GCA).

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on January 21, 2017, in accordance with 21 CFR 601.2(a).

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PHUONG N TON
12/05/2016