

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125472Orig1s018

Trade Name: ACTEMRA

Generic or Proper Name: tocilizumab injection for subcutaneous use

Sponsor: Genentech, Inc.

Approval Date: September 23, 2016

Change: For the inclusion of language regarding the improvement in general health status, assessed by the Short Form Health Survey (SF-36).

CENTER FOR DRUG EVALUATION AND RESEARCH

125472Orig1s018

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

APPROVAL LETTER



BLA 125276/S-107
BLA 125472/S-018

SUPPLEMENT APPROVAL

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

Attention: Karen R. Terry
Program Director, Regulatory

Dear Ms. Terry:

Please refer to your Supplemental Biologics License Applications (sBLAs), dated November 24, 2015, received November 24, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for BLA 125276/S-107, Actemra (tocilizumab) Injection for intravenous use, 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL, and BLA 125472/S-018, Actemra (tocilizumab) Injection for subcutaneous use, 162 mg/0.9 mL.

These Prior Approval supplemental biologics applications provide the inclusion of language regarding the improvement in general health status, assessed by the Short Form Health Survey (SF-36).

APPROVAL & LABELING

We have completed our review of these supplemental applications, 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 package insert, 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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/

SARAH K YIM
09/23/2016
Signing for Badrul Chowdhury, M.D., Ph.D.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

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)

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).

Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.2)

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

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.3)

- 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

Polyarticular Juvenile Idiopathic Arthritis (2.2)

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 (2.3)

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 (2.4)

- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm³, platelet count below 100,000 per mm³, 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 (2.5)

- For adults, PJIA and SJIA patients at or above 30 kg, dilute to 100 mL in 0.9% Sodium Chloride for intravenous infusion using aseptic technique.
- For PJIA and SJIA patients less than 30 kg, dilute to 50 mL in 0.9% 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 (2.6)

- Follow the Instructions for Use for prefilled syringe

Dose Modifications (2.7)

- 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. (2.7, 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. (6.1)

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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2016

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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 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.

1.3 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 (2.7)*, *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 thrombocytopenia [see *Dosage and Administration (2.7)*, *Warnings and Precautions (5.3)*, and *Adverse Reactions (6.2)*].

2.2 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 (2.7)*].
- Subcutaneous administration is not approved for PJIA.

2.3 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 (2.7)*].
- Subcutaneous administration is not approved for SJIA.

2.4 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 mm³, platelet count below 100,000 per mm³, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).

2.5 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% 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% 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, 2.2, 2.3)*].

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 Sodium Chloride infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.

- The fully diluted ACTEMRA solutions for infusion 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. 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.

2.6 Preparation and Administration Instructions for Subcutaneous Injection for RA

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

- 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.

2.7 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

Liver Enzyme Abnormalities [see Warnings and Precautions (5.3)]:	
Lab Value	Recommendation
Greater than 1 to 3x ULN	<p>Dose modify concomitant DMARDs if appropriate</p> <p>For persistent increases in this range:</p> <ul style="list-style-type: none"> • 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 mm³)	Recommendation
ANC greater than 1000	Maintain dose
ANC 500 to 1000	Hold ACTEMRA dosing When ANC greater than 1000 cells per mm ³ : <ul style="list-style-type: none"> • 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 mm³)	Recommendation
50,000 to 100,000	Hold ACTEMRA dosing When platelet count is greater than 100,000 cells per mm ³ : <ul style="list-style-type: none"> • 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 for rheumatoid arthritis. 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 (2.4), 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 RA patients. 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

Rheumatoid Arthritis

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 mm³. In patients who develop an absolute neutrophil count less than 500 per mm³ 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 (2.7)*].

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 mm³. In patients who develop a platelet count less than 50,000 per mm³ 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 (2.7)*].

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 (2.7)]*.

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 RA [*see Dosage and Administration (2.7)*].

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 [*see 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 arthritis 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 PJIA and SJIA 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 mm³ 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 mm³ occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500 per mm³ 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 mm³ 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 mm³ 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 (2.5)*]. 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					
	ACTEMRA 8 mg per kg MONOTHERAPY	Methotrexate	ACTEMRA 4 mg per kg + DMARDs	ACTEMRA 8 mg per kg + DMARDs	Placebo + DMARDs
Preferred Term	N = 288 (%)	N = 284 (%)	N = 774 (%)	N = 1582 (%)	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 $1 \times 10^9/L$ 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 $1 \times 10^9/L$ 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 $\leq 50 \times 10^3/mcL$.

Elevated Liver Enzymes

During routine laboratory monitoring in the 6-month controlled clinical trials, elevation in ALT or AST $\geq 3 \times$ 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.

Lipids

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 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 6.4)*].

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 6.4)*].

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 1×10^9 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 50×10^3 per mL 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%).

6.4 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 1×10^9 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 100×10^3 per mL.

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.

6.5 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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 Other Drugs for Treatment of Rheumatoid Arthritis

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 per 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)*].

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 effects 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 renal impairment. ACTEMRA has not been studied in patients with moderate to 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 IgG1 κ (gamma 1, kappa) subclass with a typical H₂L₂ 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 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 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 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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} .

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 (\pm SD) $AUC_{4\text{weeks}}$, 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 (\pm SD) $AUC_{4\text{weeks}}$, 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 $AUC_{4\text{weeks}}$, 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 (\pm SD) $AUC_{2\text{weeks}}$, 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 rheumatoid arthritis patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 0.8.

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 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

The total clearance of tocilizumab is concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance in the population pharmacokinetic analysis was estimated to be 12.5 mL per h in RA, 5.8 mL per h in pediatric patients with PJIA, and 7.1 mL per h in pediatric patients with SJIA. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab is concentration-dependent. For IV administration, 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, 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.

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 less than 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 showed that age, gender and race did not affect the pharmacokinetics of tocilizumab. Linear clearance was found to increase with body size. 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.

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 patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance less than 80 mL per min and at or above 50 mL per min based on Cockcroft-Gault) did not impact the pharmacokinetics of tocilizumab. No dose adjustment is required in patients with mild 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		
	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
Response Rate													
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	
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	
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	
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	

^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

Component (mean)	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	
	Baseline	Week 24 ^a	Baseline	Week 24 ^a	Baseline	Week 24	Baseline	Week 24 ^a	Baseline	Week 24 ^a	Baseline	Week 24
Number of tender joints (0-68)	33	19 -7.0 (-10.0, -4.1)	32	14.5 -9.6 (-12.6, -6.7)	33	25	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
Number of swollen joints (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
Pain ^b	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
Patient global assessment ^b	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45	70	46 -10.0 (-20.3, 0.3)	70	36 -17.4 (-27.8, -7.0)	71	51
Physician global assessment ^b	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
Disability index (HAQ) ^c	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg per dL)	2.79	1.17 -1.30 (-2.0, -0.59)	2.61	0.25 -2.156 (-2.86, -1.46)	2.36	1.89	3.11	1.77 -1.34 (-2.5, -0.15)	2.80	0.28 -2.52 (-3.72, -1.32)	3.705	3.06

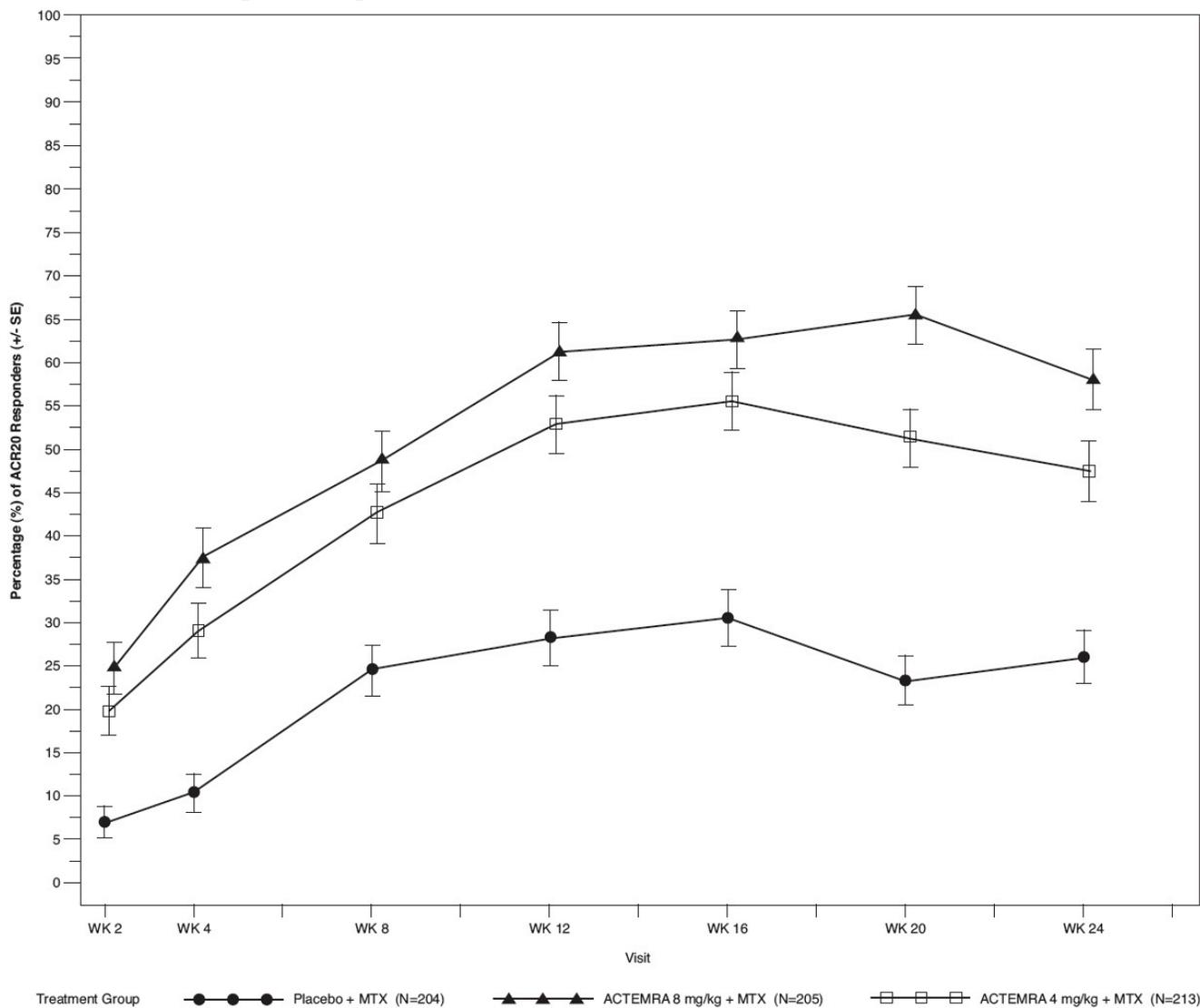
^a Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

^b Visual analog scale: 0 = best, 100 = worst

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

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

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



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

Radiographic Response

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

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

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

* Week 52 analysis employs linearly extrapolated data for patients after escape, withdrawal, or loss to follow up.

** Difference between the adjusted means (ACTEMRA + MTX - Placebo + MTX)

SD = standard deviation

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

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

Health Related Outcomes

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

Other Health-Related Outcomes

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

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 ≥ 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 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.

14.4 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 8**.

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

^aThe 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 2°C to 8°C (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

Read this Medication Guide before you start ACTEMRA, before each infusion, or each time you get a prescription refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

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 doctor should test you for TB before starting ACTEMRA.

- Your doctor 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
 - muscle aches
 - cough
 - shortness of breath
 - blood in phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinating more often than normal
 - feel very tired
- 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, after the first 4 to 8 weeks for rheumatoid arthritis (after which tests should be done every 3 months), every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA during treatment 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.

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.

- 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.

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.
- People with active polyarticular juvenile idiopathic arthritis (PJIA) ages 2 and above.
- People with active systemic juvenile idiopathic arthritis (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.

Who should not take ACTEMRA?

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.

What should I tell my healthcare provider before receiving ACTEMRA?

ACTEMRA may not be right for you. **Before receiving ACTEMRA, tell your healthcare provider 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 breast-feed or are breast-feeding. 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 and non-prescription 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 doctor 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.
- If you miss a scheduled dose of ACTEMRA, ask your healthcare provider when to schedule your next infusion.
- 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:

- **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 doctor 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 doctor 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:
 - feel very tired
 - skin or eyes look yellow
 - little or no appetite
 - vomiting
 - clay-colored bowel movements
 - fevers
 - chills
 - stomach discomfort
 - muscle aches
 - dark urine
 - skin rash

- **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:
 - shortness of breath or trouble breathing
 - swelling of the lips, tongue, or face
 - chest pain
 - feeling dizzy or faint
 - moderate or severe abdominal pain or vomiting
- **Nervous system problems.** While rare, Multiple Sclerosis has been diagnosed in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.

Common side effects of ACTEMRA include:

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

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of ACTEMRA. For more information, ask your healthcare provider or pharmacist.

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 ACTEMRA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about ACTEMRA.

If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ACTEMRA that is written for health professionals.

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

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.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

MG Revised: October 2013

ACTEMRA is a registered trademark of Chugai Seiyaku Kabushiki Kaisha Corp., a member of the Roche Group.

Genentech, Inc.

A Member of the Roche Group

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Summary Review
NDA/BLA # Supplement #	sBLA 125276, supplement 107 (Actemra intravenous); sBLA 125472, supplement 18 (Actemra subcutaneous)
Applicant Name	Genentech/Hoffman-La Roche, Ltd.
Date of Submission	November 24, 2015
PDUFA Goal Date	September 24, 2016
Proprietary Name / Established (USAN) Name	Actemra / Tocilizumab
Dosage Forms / Strength	No new dosage forms or strengths. Currently approved: --Single-use vials of Actemra (20 mg/mL) for intravenous administration in 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL vials --Single-use prefilled syringe (PFS) providing 162 mg/0.9 mL
Proposed Change(s)	1. Inclusion of SF-36 data from the SC and IV studies in RA
Action:	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
CDTL Review	Nikolay Nikolov, MD
Medical Officer Review	Rachel Glaser, MD
Statistical Review	Robert Abugov, PhD; Gregory Levin, PhD
Pharmacology Toxicology Review	Brett Jones, PhD; Timothy Robison, PhD
DPMH Review	Christos Mastroyannis, MD; Tamara Johnson, MD, MS; Lynne Yao, MD

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

DPMH=Division of Pediatric and Maternal Health

1. Introduction

Genentech/Hoffman La-Roche submitted this supplemental biologics license application (sBLA) for re-consideration for inclusion of the health status instrument Short Form-36 (SF-36) results in the Clinical Studies section of the product label for Actemra (tocilizumab) based on data submitted in the original BLA. The original BLA for Actemra in rheumatoid arthritis (RA) was approved in January 2010, and the subcutaneous (SC) Actemra BLA was approved

in October 2013, but at those times the SF-36 findings were not included in the product labeling. This summary review will provide an overview of the application, and reasoning and rationale for inclusion of SF -36 results data in the Clinical Studies section of the product labeling.

2. Background

The approval of most of the recent products approved for Rheumatoid arthritis (RA) was supported by establishing efficacy in key domains of the disease, namely clinical response and physical function, based on internationally agreed upon endpoints. Clinical response has been assessed by ACR response rates¹ and measures of low disease activity, such as DAS28² less than 2.6, have been used as supportive evidence of efficacy in this domain. For physical function, HAQ-DI³ has been typically used to demonstrate an improvement in physical function, and the Physical Component Summary (PCS) of the SF-36 was historically used as supportive evidence of efficacy in this domain.

The SF-36 is a multi-purpose, short-form health survey. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It was originally developed to satisfy minimum psychometric standards for group comparisons in 1980s and 90s and has been used in health planning and policy, and health services evaluation in an era of cost containment, and has subsequently been validated in many diseases, including RA and other rheumatic conditions. This is the most widely used health status questionnaire in the world (used in ~ 4000 publications).

The SF-36 consists of 36 questions relating to either physical or mental health. The questions are divided into eight domains: four for physical health (physical health, bodily pain, physical functioning and physical role limitations) and four for mental health (mental health, vitality, social functioning and emotional role limitation). The eight domains are age, and gender adjusted and scored 0 (severe impairment) – 100 (no impairment). Subsequently, two psychometrically-based summary measures, physical component summary (PCS) and mental component summary (MCS), were developed to simplify the analysis and interpretation of the SF-36. PCS measures how decrements in physical function affect day to day activities and MCS measures the impact of mental affect and symptoms of pain on quality of life. The PCS and MCS are reported based on normative-based scoring.

¹ ACR20 (50, 70) response criteria — American College of Rheumatology response criteria is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50, 70) percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, physician global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index (HAQ-DI)), and acute phase reactants.

² DAS28 — Disease Activity Score 28 is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis.

³ HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

Prior to 2008, SF-36 was included in the labeling for RA products, as supportive data for the Health Assessment Questionnaire Disability Index (HAQ-DI) for the claim of improvement in physical function. Between 2008 and 2013, the Agency denied proposed labeling for SF-36 due to concerns raised by the Study Endpoints and Labeling Development (SEALD) team about the SF-36 instrument in general and particularly about the use of the SF-36 physical component summary (PCS) score and mental component summary (MCS) score in RA product labels. These concerns included: 1) SF-36 is generic health survey that has not been shown to represent health-related quality of life in RA, and 2) PCS and MCS are composite measures of weighted scores from all 8 subconcepts/domains, are not independent, and cannot be described in a way that is meaningful. At the time, the review division—Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)—determined that the HAQ-DI alone would be adequate to support an improvement in physical function claim, and that the SF-36 PCS was not necessary. As a result, SF-36 information from four RA products—Simponi (golimumab), Cimzia (certolizumab), Actemra (tocilizumab), and Xeljanz (tofacitinib)—was not included in the product labeling.

Since then, based on continued pushback from the rheumatology academic community, the Agency's thinking on the utility of SF-36 in RA product development and labeling has evolved. The pertinent regulatory history of SF-36, as captured in Dr. Glaser's clinical review, was extensively discussed at an internal Regulatory Briefing on September 20, 2013 and the decision of the current review Division (DPARP) to re-implement SF-36 in RA product labeling to support a separate claim of improvement in general health status was supported by CDER senior management. Subsequently, information on SF-36, including the PCS, MCS, and the 8 domains, was included in the Xeljanz labeling (NDA 203,214, supplement 002 approved in November 2013) and in the Simponi Aria labeling (BLA 125,433, supplement 0014 approved in August 2015) to support general health status claims. Following these precedents, Genentech/Hoffman La-Roche submitted this request for re-consideration for inclusion of the SF-36 data, which had been submitted in the original tocilizumab BLAs.

3. CMC/Device

No new CMC information was submitted with these supplemental applications and there are no outstanding CMC issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was submitted with these supplements. However, the Applicant submitted updates to the labeling to comply with the PLLR requirements.⁴ The proposed changes were reviewed by the Pharmacology and Toxicology review team. The team provided labeling recommendations to Section 8, Use in Specific Populations, relevant to the proposed PLLR content based on the available data from the submissions and published literature. The Pharmacology and Toxicology review team also updated Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, based on data from the currently available published literature.

⁴ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf>

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics information was submitted with these supplements. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The data supporting the proposed labeling for the SF-36 are derived from the original 5 randomized controlled trials that were submitted in the original IV tocilizumab BLA, as well as the 2 randomized controlled trials that were submitted in support of the SC tocilizumab approval. Key features of these trials are summarized in Table 1 and Table 2 below.

Table 1: Key Design Features of the Pivotal IV Tocilizumab RA Studies

Study	Design/ Duration	Population/N	Dose Regimen	Primary Endpoint
WA17822	R, DB, PC 24 weeks	Moderate to severe active RA in MTX-IR 623	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): TCZ 8 mg/kg	ACR20 at Wk 24
WA17823	R, DB, PC 52 weeks	Moderate to severe active RA in MTX-IR 1196	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): Blinded TCZ 4 mg/kg (from PBO) or TCZ 8 mg/kg (from 4 mg/kg) After Wk 24: TCZ 8 mg/kg	ACR20 at Wk 24
WA17824	R, DB, DD, PC 24 weeks	Active RA in MTX naïve or MTX discontinued 673	TCZ 8 mg/kg IV q4 wks + PBO PO /wk PBO IV q4 wks + MTX PO 7.5-20 mg/wk Substudy: PBO for 8 wks, then TCZ 8 mg/kg IV q4 wks for 16 wks Escape (Substudy, up to Wk 8): TCZ 8 mg/kg	ACR20 at Wk 24
WA18062	R, DB, PC 24 weeks	Moderate to severe active RA in TNF-IR 499	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): TCZ 8 mg/kg	ACR20 at Wk 24
WA18063	R, DB, PC 24 weeks	Moderate to severe active RA in DMARD-IR 1220	TCZ 8 mg/kg IV q4wks + standard DMARDs PBO IV q4 wks + standard DMARDs Escape (Wk 16): Adjustment of background DMARDs	ACR20 at Wk 24

DB=double blind, R = randomized, PC = placebo controlled, DD = double dummy, OL = open label, IR = inadequate responders, TCZ = tocilizumab, MTX = methotrexate, PBO = placebo

Source: Adapted from BLA 125276 Module 2.7.3 Summary of Efficacy Tables 1, 4

Table 2: Key Design Features of the Pivotal SC Tocilizumab RA Studies

Study	Design/ Duration	Population/N	Dose Regimen	Primary Endpoint
WA22762	R, DB, DD, AC, PG 24 weeks	Moderate to severe active RA in DMARD/ bDMARD-IR 1262	TCZ 162 mg SC qwk + PBO IV q4 wks + DMARD PBO SC qwk + TCZ 8 mg/kg IV q4wks + DMARD	ACR20 at Wk24
NA25220	R, DB, PC 24 weeks	Moderate to severe active RA in DMARD/ bDMARD-IR 656	TCZ 162 mg q2wk + DMARD PBO SC q2wk + DMARD Escape (Wk 12-24): TCZ 162 mg SC qwk	ACR20 at Wk24

DB=double blind, R = randomized, PC = placebo controlled, DD = double dummy, AC= active controlled, PG= parallel group, IR = inadequate responders, DMARD = disease modifying anti-rheumatic drug, TCZ = tocilizumab, PBO = placebo
Source: Adapted from BLA 125472 Module 2.7.3 Summary of Efficacy Table 1

SF-36 PCS and MCS summary scores were secondary endpoints in the IV TCZ studies WA17822, WA17823, WA17824, WA18062, and WA18063, and SC TCZ Study NA25220. In SC TCZ Study WA25220, these endpoints were defined as quality of life and exploratory endpoints. Minimal clinically important difference (MCID) of 2.5-5 points for the composite scores and 5-10 points for the domain scores have been proposed in the literature.⁵

IV Tocilizumab Studies

At Week 24, for the physical component summary, PCS (Table 3) and the physical function domain, all studies showed differences between tocilizumab 4 mg/kg IV and placebo and between tocilizumab 8 mg/kg IV and placebo (data not shown). For all other domains, as well as for mental component summary, MCS (Table 3), trends consistently favored treatment (data not shown). Only one point estimate favored placebo rather than treatment, the comparison between tocilizumab 4 mg/kg IV and placebo in the social function domain for Study WA17823; even then the point estimate comparing tocilizumab 8 mg/kg IV and placebo for that domain favored treatment.

⁵ Strand V and Singh J, Am J Manag Care. 2008;14(4):239-253

Table 3: Adjusted Mean Change in PCS and MCS Scores at Week 24

Study	SF-36 Measure	PBO + MTX/DMARD	TCZ 4 mg/kg + MTX/DMARD	TCZ 8 mg/kg + MTX/DMARD
WA17822	PCS	5.0	9.7*	9.5*
	MCS	2.7	5.7*	7.3*
WA17823	PCS	5.56	7.84*	8.15*
	MCS	2.84	3.23	4.18
WA17824	PCS	7.77	n/a	9.78**
	MCS	4.81	n/a	6.77
WA18062	PCS	2.22	7.09*	8.02*
	MCS	4.07	4.46	4.06
WA18063	PCS	4.08	n/a	8.87*
	MCS	2.26	n/a	5.31*

*p < 0.05

**For Study 18724, lower bound of 95% CI > 0

Source: Adapted from Applicant submission BLA 125276, CSR from Studies WA17822, WA17823, WA17824, WA18062, WA18063

SC Tocilizumab Studies

In Study NA25220, there was greater improvement in both PCS and MCS in the group that received SC TCZ 162 mg q2w + DMARD, as compared to the group that received placebo + DMARD. This was supported by statistically significant improvement in the 8 domains in the tocilizumab treatment group as compared to the placebo group. In Study WA22762, mean change from baseline in SF-36 composite scores were generally comparable across treatments with TCZ IV 8 mg/kg + DMARD and TCZ 162 mg SC qw + DMARD (Table 4 below). The change in SF-36 composite scores exceeded the minimum clinically important difference for all tocilizumab treatment groups, but not for the placebo + DMARD group in Study NA25220.

Table 4: Mean Change in PCS and MCS Scores at Week 24

Mean Change at Wk24	Study WA22762		Study NA25220	
	TCZ 162 mg SC qw + DMARD	TCZ 8 mg/kg + DMARD	PBO SC q2w + DMARD	TCZ 162 mg SC q2w + DMARD
PCS	9.33	9.61	4.32	7.16*
MCS	6.23	6.75	3.01	6.12*

*p-value < 0.05

Source: Adapted from Applicant submission BLA 125472, Summary of Clinical Efficacy Table 35

The statistical analyses of the data, handling of missing data, and sensitivity analyses were reviewed by the FDA statistical review team, and no major statistical issues were identified. The clinical and statistical review teams were in agreement that the data adequately supports inclusion of SF-36 results into the clinical studies section of the Actemra label.

8. Safety

No new safety information was submitted with these supplements. The safety information from tocilizumab development was reviewed in detail with the original BLA submissions.

9. Advisory Committee Meeting

No Advisory Committee was warranted nor convened for these supplements.

10. Pediatrics

No new issues were raised by these supplements. The requirements of the Pediatric Research Equity Act (PREA) were addressed in the original BLAs.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The applicant's proposed labeling will be revised for consistency with FDA's current approach to SF-36 labeling, which identifies SF-36 as a general health status instrument and will include results for the PCS, MCS, and the 8 domains. Labeling changes to comply with the Pregnancy and Lactation Labeling Rule (PLLR) will also be implemented, as per recommendations from the pharmacology/toxicology review team and consultants from the Division of Pediatric and Maternal Health (DPMH).

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The action on the supplemental applications will be Approval.

- **Risk Benefit Assessment**

The overall risk-benefit profile of tocilizumab in RA remains favorable, as determined at the time of the original BLA approvals and is not altered on the basis of this submission. The current submission supports the addition of SF-36 results in Section 14 of the prescribing information. Although the risks of tocilizumab are not minimal, these are balanced by a number of clinical benefits, which include reduction in patient signs and symptoms and disease activity, structural progression, improvement in physical functioning, and general health status.

- **Postmarketing Risk Evaluation and Mitigation Strategies**

Risk Evaluation and Mitigation Strategies (REMS) are not warranted.

- **Other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are warranted.

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/s/

SARAH K YIM
09/23/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	Electronic Stamp
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #, Supplement#	125276, Supplement 107 125472, Supplement 018
Applicant	Genentech, Inc.
Date of Submission	November 24, 2015
PDUFA Goal Date	September 24, 2016
Proprietary Name / Established (USAN) names	Actemra/tocilizumab
Dosage forms / Strength	<ul style="list-style-type: none">• Single use vials of 20 mg/mL: 80 mg/4mL, 200 mg/10mL, 400 mg/20 mL, for IV infusion• (b) (4)mL ready-to-use, single-use prefilled syringe (PFS) with a needle safety device for subcutaneous administration <p>(No new dosage forms or strengths were proposed with these supplements)</p>
Proposed Claim	(b) (4)
Recommended:	Approval, with Revisions to Proposed Label

1. Introduction

Genentech submitted these biologics license applications (BLA) supplements for the Agency's re-consideration for inclusion of SF-36 findings in the product labeling based on data submitted in the original BLAs. BLA 125276 for intravenous (IV) tocilizumab (TCZ) for the treatment of patients with rheumatoid arthritis (RA) was approved in January 2010 and BLA 125472 for subcutaneous (SC) tocilizumab for the treatment of patients with RA was

originally approved in October 2013. At the time of the original approvals, the SF-36 findings were not included in the product labeling. This summary review provides an overview of the application, and reasoning and rationale for inclusion of SF-36 data in the Section 14, Clinical Studies of the product labeling. In addition, with these supplements, the Actemra labeling is updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) requirements.¹

The overall clinical efficacy and risk-benefit analysis of tocilizumab remain consistent with the original BLAs. Further, the Agency's analyses of the SF-36 data are in general agreement with the Applicant's analyses. Thus, the SF-36 data submitted are adequate to support inclusion in product labeling.

2. Background

Rheumatoid arthritis (RA) is a chronic symmetric inflammatory polyarthritis, affecting approximately 1% of the adult population worldwide. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system.ⁱ Thanks to the advances in our understanding of the disease and the established drug development pathway, many effective treatments have been developed and approved for RA. The approval of most of these products was supported by establishing efficacy in the key domains of the disease, namely clinical response and physical function based on internationally agreed upon endpoints. The clinical response has been assessed by ACR response rates² and measures of low disease activity, such as DAS28³ less than 2.6, have been used as supportive evidence of efficacy in this domain. For physical function, HAQ-DI⁴ is usually used to demonstrate an improvement in physical function, and the SF-36, and more specifically the Physical Component Summary (PCS) has been historically used as supportive evidence of efficacy in this domain. Other outcomes that have important implications for patients and health care providers, such as radiographic endpoints, have been used to provide further characterization of the efficacy of a drug product and its utility in clinical practice.

However, there has been a recent emphasis on studying the effects of treatments on aspects of the disease that are important to patients and are not captured by other outcomes.ⁱⁱ These measures include patient-reported outcomes (PROs) such as the generic SF-36 health survey, the subject of these supplemental applications.

¹ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf>

² ACR20 (50, 70) response criteria — American College of Rheumatology response criteria is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50, 70) percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, physician global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index (HAQ-DI)), and acute phase reactants.

³ DAS28 — Disease Activity Score 28 is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis.

⁴ HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

Prior to 2008, SF-36 was included in the labeling for RA products, as supportive data for the Health Assessment Questionnaire Disability Index (HAQ-DI) for the claim of improvement in physical function. Between 2008 and 2013, the Agency denied proposed labeling for SF-36 due to concerns raised by the Study Endpoints and Labeling Development (SEALD) team about the SF-36 instrument and in particular the use of the SF-36 physical component summary (PCS) score and mental component summary (MCS) score in RA product labels. At the time, the Division of Anesthesia, Analgesia, and Rheumatology Products, DAARP, (the review Division then) determined that SF-36 was no longer needed to supplement the data from the HAQ-DI in supporting the improvement in physical function claim. As a result, SF-36 information from four RA products, golimumab/Simponi, certolizumab/Cimzia, tocilizumab/Actemra, and tofacitinib/Xeljanz, was not included in the product labeling. Since then, based on continued pushback from the rheumatology academic community, the Agency's thinking on the utility of SF-36 in RA product development and labeling has evolved. The pertinent regulatory history of SF-36, as captured in Dr. Glaser's clinical review, was extensively discussed at an internal Regulatory Briefing on September 20, 2013 and the decision of the current review Division (DPARP) to re-implement SF-36 in RA product labeling to support a claim of improvement in general health status was supported by CDER senior management. Subsequently, information on SF-36, including on PCS, MCS, and the 8 domains, was included in the Xeljanz labeling (NDA 203,214, supplement 002 approved in November 2013) and in the Simponi Aria labeling (BLA 125,433, supplement 0014 approved in August 2015) to support general health status claims. Following these precedents, Genentech submitted this request for re-consideration for inclusion of the SF-36 data, submitted in the original tocilizumab BLAs.

The SF-36 was not specifically discussed with the Applicant during pre-submission interactions. However, SF-36 was collected as a patient-reported outcome of interest in the protocols of phase 3 confirmatory clinical studies in both the subcutaneous and intravenous tocilizumab clinical programs and submitted to the respective applications.

3. CMC/Device

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 BLAs.

4. Nonclinical Pharmacology/Toxicology

*Pharmacology and Toxicology Reviewer: Brett Jones, Ph.D.,
Pharmacology and Toxicology Team Leader: Timothy Robison, Ph.D.*

No new non-clinical pharmacology/toxicology information was submitted with this supplement. However, the Applicant submitted updates to the labeling to comply with the

PLLR requirements.⁵ The proposed changes were reviewed by the Pharmacology and Toxicology review team. The team provided labeling recommendations to Section 8, Use in Specific Populations, relevant to the proposed PLLR content based on the available data from the submissions and published literature. The Pharmacology and Toxicology review team also updated Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, based on data from the currently available published literature. I concur with their recommended labeling changes.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this supplement. Such information is not required for the regulatory decision on these supplements. The relevant information was previously reviewed in the original BLAs.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Statistical Reviewer: Robert Abugov, Ph.D.,
Statistical Team Leader: Gregory Levin, Ph.D.
Clinical Reviewer: Rachel Glaser, M.D.

Overview of the Clinical Program

Five randomized placebo-controlled trials have been submitted as the primary evidence of efficacy and safety of IV tocilizumab and two randomized placebo-controlled trials have been submitted in support of SC tocilizumab, as summarized in the text and in Table 1 and Table 2 below.

IV Tocilizumab Studies in RA

The IV tocilizumab program in RA comprised of 5 randomized, double-blind controlled trials of TCZ in 4211 RA patients with moderately to severely active disease. Four were placebo-controlled trials (WA17822, WA17823, WA18062 and WA18063), and one was a non-inferiority trial (WA17824) comparing TCZ versus methotrexate (MTX). The trials studied the range of RA patients, from those with less refractory disease that had not previously required MTX (WA17824) to more typical RA patients who had inadequate response to MTX and other DMARDs (WA17822, WA17823, and WA18063) and more refractory RA patients

⁵ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf>

who had inadequate response to TNF inhibitors (WA18062). Three of the trials assessed TCZ vs. placebo as add-on therapy to background MTX (WA17822, WA17823, WA18062), one trial assessed TCZ vs. placebo as add-on therapy to a range of commonly used DMARDs including MTX (WA18063), and one trial assessed TCZ 8 mg/kg monotherapy vs. optimized MTX monotherapy (WA17824). Three of the trials also included a treatment arm with TCZ 4 mg/kg as add-on therapy (WA17822, WA17823, and WA18062).

Table 1: Key Design Features of the Pivotal IV Tocilizumab RA Studies

Study	Design/ Duration	Population/N	Dose Regimen	Primary Endpoint
WA17822	R, DB, PC 24 weeks	Moderate to severe active RA in MTX-IR 623	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): TCZ 8 mg/kg	ACR20 at Wk 24
WA17823	R, DB, PC 52 weeks	Moderate to severe active RA in MTX-IR 1196	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): Blinded TCZ 4 mg/kg (from PBO) or TCZ 8 mg/kg (from 4 mg/kg) After Wk 24: TCZ 8 mg/kg	ACR20 at Wk 24
WA17824	R, DB, DD, PC 24 weeks	Active RA in MTX naïve or MTX discontinued 673	TCZ 8 mg/kg IV q4 wks + PBO PO /wk PBO IV q4 wks + MTX PO 7.5-20 mg/wk Substudy: PBO for 8 wks, then TCZ 8 mg/kg IV q4 wks for 16 wks Escape (Substudy, up to Wk 8): TCZ 8 mg/kg	ACR20 at Wk 24
WA18062	R, DB, PC 24 weeks	Moderate to severe active RA in TNF-IR 499	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): TCZ 8 mg/kg	ACR20 at Wk 24
WA18063	R, DB, PC 24 weeks	Moderate to severe active RA in DMARD-IR 1220	TCZ 8 mg/kg IV q4wks + standard DMARDs PBO IV q4 wks + standard DMARDs Escape (Wk 16): Adjustment of background DMARDs	ACR20 at Wk 24

DB=double blind, R = randomized, PC = placebo controlled, DD = double dummy, OL = open label, IR = inadequate responders, TCZ = tocilizumab, MTX = methotrexate, PBO = placebo

Source: Adapted from BLA 125276 Module 2.7.3 Summary of Efficacy Tables 1, 4

SC Tocilizumab Studies in RA

The data in this submission are derived from two phase 3 randomized, double-blind controlled trials of TCZ in 1,918 (SC = 1,068; IV = 850) adult RA patients with moderately to severely active disease who have had an inadequate response to one or more DMARDs. Study

WA22762 was a non-inferiority study comparing TCZ SC 162mg qw (high dose) to TCZ IV 8mg/kg q4w (high dose). Study NA25220 was a superiority study comparing TCZ SC 162mg q2w (low dose) to placebo. All treatment arms included a background of DMARDs therapy. The primary endpoint was ACR20 at week 24.

Table 2: Key Design Features of the Pivotal SC Tocilizumab RA Studies

Study	Design/ Duration	Population/N	Dose Regimen	Primary Endpoint
WA22762	R, DB, DD, AC, PG 24 weeks	Moderate to severe active RA in DMARD/ bDMARD-IR 1262	TCZ 162 mg SC qwk + PBO IV q4 wks + DMARD PBO SC qwk + TCZ 8 mg/kg IV q4wks + DMARD	ACR20 at Wk24
NA25220	R, DB, PC 24 weeks	Moderate to severe active RA in DMARD/ bDMARD-IR 656	TCZ 162 mg q2wk + DMARD PBO SC q2wk + DMARD Escape (Wk 12-24): TCZ 162 mg SC qwk	ACR20 at Wk24

DB=double blind, R = randomized, PC = placebo controlled, DD = double dummy, AC= active controlled, PG= parallel group, IR = inadequate responders, DMARD = disease modifying anti-rheumatic drug, TCZ = tocilizumab, PBO = placebo
 Source: Adapted from BLA 125472 Module 2.7.3 Summary of Efficacy Table 1

Overview of Efficacy

Treatment with IV and SC tocilizumab was shown to effectively reduce signs and symptoms of active arthritis as measured by ACR 20 response rate at Week 24 as the primary endpoint. Secondary endpoints in the IV program included ACR 50 and 70 responses, changes from baseline in individual parameters of the ACR core set, change in DAS28, DAS28 remission, EULAR response, change in hemoglobin, ACRn, HAQ, and other measures. Secondary endpoints in the SC program included ACR 50 and 70 responses, DAS28 remission, and proportion of patients with decrease in HAQ-DI ≥ 0.3 . In addition, inhibition of progression of radiographic changes was evaluated in Study WA17823 and Study NA25220.

SF-36 PCS and MCS summary scores were secondary endpoints in the IV TCZ studies WA17822, WA17823, WA17824, WA18062, and WA18063, and SC TCZ Study NA25220. In SC TCZ Study WA25220, these endpoints were defined as quality of life and exploratory endpoints. Minimal clinically important difference (MCID) of 2.5-5 points for the composite scores and 5-10 points for the domain scores have been proposed in the literature.ⁱⁱⁱ Results of SF-36 are discussed in detail below. Detailed protocol design, study conduct and results of endpoints such as ACR responses and HAQ-DI for individual studies were reviewed in the original BLA applications and are not discussed in this document.

Statistical Analysis of SF-36 Data

The SF-36 data were collected and analyzed for randomized subjects in both IV and SC tocilizumab programs. In the IV tocilizumab program, changes from baseline in the PCS and MCS scores of SF-36 were compared between groups using an ANOVA model with the stratification factors applied at randomization. Analyses of SF-36 for non-inferiority study WA18724 included patients in the per-protocol population, defined as those patients who met inclusion criteria and remained on randomized treatment without rescue medication or protocol violations. Analyses of other studies included the intent to treat population, defined as all randomized patients who received at least one dose of study medication. A two-sided 5% significance level was used. To control for multiplicity, secondary efficacy parameters, including SF-36 PCS and MCS at 24 weeks, were hierarchically ordered and tested in a pre-defined sequential order.

Handling of SF-36 Missing Data

For partially answered questionnaires, if more than 50% of the items within each domain were unanswered, the domain score was assigned to missing and only observed values, including data collected after patient escape or withdrawal from randomized treatment, were used in the analyses. If at least 50% of the items within each domain were answered, the missing item scores were imputed with the average score across the completed items in the same scale. Aggregated scores were computed after the imputation rule was applied to the component domains, but set to missing if any domain was missing. Patients with missing aggregate scores were excluded from analyses and summary statistics. If a subject met the early escape criteria, the data collected at the escape visit was used as is and the SF-36 score was set to missing subsequently; no imputations of missing data were conducted. A sensitivity analysis utilizing a last observation carried forward method was conducted.

Patient Disposition

No notable imbalances in demographic and baseline characteristics between treatment groups were found as described in the original BLA submissions.

Results of SF-36 Data

IV Tocilizumab Studies

At Week 24, for the physical component summary, PCS (Table 3) and the physical function domain, all studies showed differences between tocilizumab 4 mg/kg IV and placebo and between tocilizumab 8 mg/kg IV and placebo (data not shown). For all other domains, as well as for mental component summary, MCS (Table 3), trends consistently favored treatment (data not shown). Only one point estimate favored placebo rather than treatment, the comparison between tocilizumab 4 mg/kg IV and placebo in the social function domain for Study WA17823; even then the point estimate comparing tocilizumab 8 mg/kg IV and placebo for that domain favored treatment.

Table 3: Adjusted Mean Change in PCS and MCS scores by IV treatment group at Week 24

Study	SF-36 Measure	PBO + MTX/DMARD	TCZ 4 mg/kg + MTX/DMARD	TCZ 8 mg/kg + MTX/DMARD
WA17822	PCS	5.0	9.7*	9.5*
	MCS	2.7	5.7*	7.3*
WA17823	PCS	5.56	7.84*	8.15*
	MCS	2.84	3.23	4.18
WA17824	PCS	7.77	n/a	9.78**
	MCS	4.81	n/a	6.77
WA18062	PCS	2.22	7.09*	8.02*
	MCS	4.07	4.46	4.06
WA18063	PCS	4.08	n/a	8.87*
	MCS	2.26	n/a	5.31*

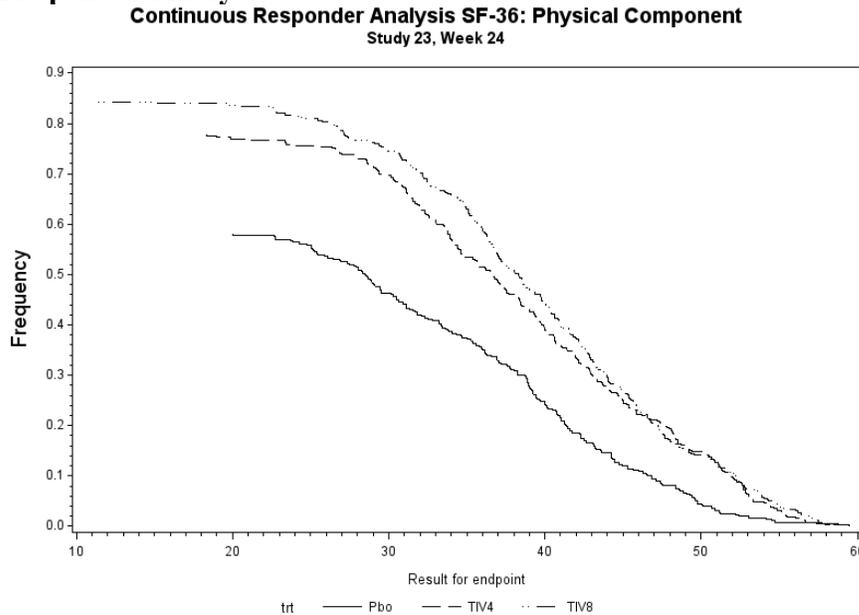
*p < 0.05

**For Study 18724, lower bound of 95% CI > 0

Source: Adapted from Applicant submission BLA 125276, CSR from Studies WA17822, WA17823, WA17824, WA18062, WA18063

Sensitivity analyses, conducted by Dr. Abugov, examined the continuous responder functions between placebo and treatment showed consistent results with the analyses of the mean change from baseline with clear separation between the two tocilizumab doses and placebo groups, as shown in Figure 1 as representative of SF-36 PCS data from Study WA17823 and in Figure 2 as representative of SF-36 MCS data from Study WA17823.

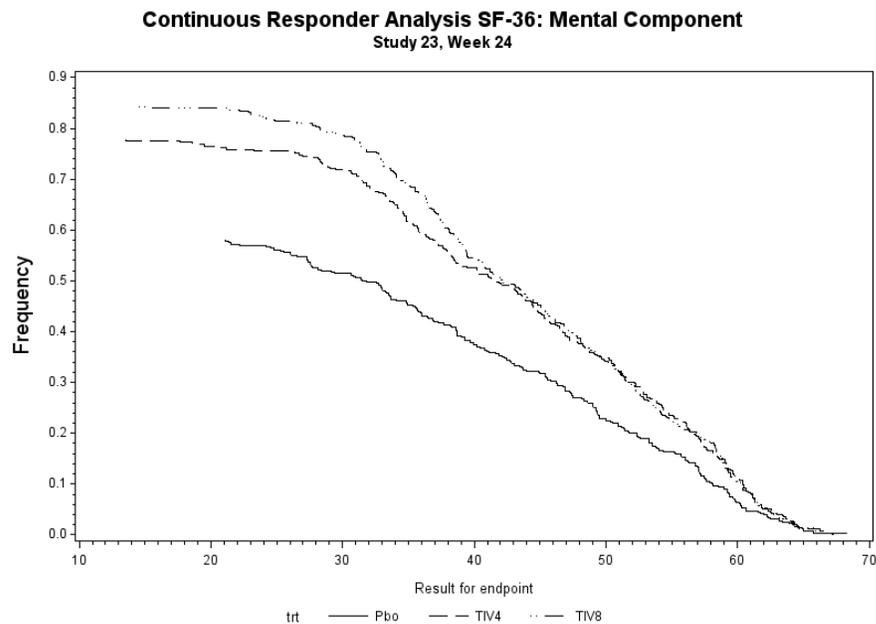
Figure 1. Change from Baseline SF-36 PCS score, Week 24, Study WA17823, Continuous Responder Analysis



Kolmogorov-Smirnov Test TIV8 vs Placebo: P-Value = 0.0290

Source: Figure adapted from Dr. Glaser's clinical review

Figure 2. Change from Baseline SF-36 MCS score, Week 24, Study WA17823, Continuous Responder Analysis



Kolmogorov-Smirnov Test TIV8 vs Placebo: P-Value = 0.8710
Source: Figure adapted from Dr. Glaser's clinical review

As noted above, minimal clinically important difference (MCID) of 2.5-5 points for the composite scores and 5-10 points for the domain scores have been proposed in the literature.

SC Tocilizumab Studies

In Study NA25220, there was greater improvement in both PCS and MCS in the group that received SC TCZ 162 mg q2w + DMARD, as compared to the group that received placebo + DMARD. This was supported by statistically significant improvement in the 8 domains in the tocilizumab treatment group as compared to the placebo group. In Study WA22762, mean change from baseline in SF-36 composite scores were generally comparable across treatments with TCZ IV 8 mg/kg + DMARD and TCZ 162 mg SC qw + DMARD (Table 4). The change in SF-36 composite scores exceeded the minimum clinically important difference for all tocilizumab treatment groups, but not for the placebo + DMARD group in Study NA25220.

Table 4: Mean Change in PCS and MCS scores by Treatment Group at Week 24 in SC Studies (ITT Population)

Mean Change at Wk24	Study WA22762		Study NA25220	
	TCZ 162 mg SC qw + DMARD	TCZ 8 mg/kg + DMARD	PBO SC q2w + DMARD	TCZ 162 mg SC q2w + DMARD
PCS	9.33	9.61	4.32	7.16*
MCS	6.23	6.75	3.01	6.12*

*p-value < 0.05

Source: Adapted from Applicant submission BLA 125472, Summary of Clinical Efficacy Table 35

- **Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL’s conclusions.**

The five IV tocilizumab studies described above showed clinically relevant and statistically significant improvements in SF-36 PCS score with treatment with tocilizumab as compared to placebo. Trends towards improvement in change from baseline in SF-36 MCS score were observed; these met statistical significance in studies WA17822 and WA18063. The improvements in MCS exceeded the minimum MCID for composite scores of 2.5 to 5 in all of the studies. Greater numerical improvement in the 8 domains was observed in the tocilizumab treatment groups as compared to the placebo treatment groups. The two SC studies demonstrate similar clinically relevant improvement in PCS and MCS with both SC and IV formulations of TCZ, both of which are superior to placebo. The FDA statistical review team analyses were inconsistent with the analyses presented by the Applicant. No important statistical issues were identified by the statistical review team. Of note, these SF-36 results are consistent with the treatment effects observed in other RA products, as described in the published literature.^{iv, v, vi, vii, viii}

Based on these results, the clinical reviewer and the statistical review team, concluded that, collectively, the SF-36 data from the phase 3 clinical studies in this submission indicate that compared to placebo, tocilizumab 4 mg/kg IV, 8 mg/kg IV, and 162 mg SC, improves PCS, MCS, and all eight SF-36 domains in patients with active RA supporting the proposed indication. I concur with this conclusion.

8. Safety

No new safety information was submitted with these supplements. The safety information from tocilizumab development was reviewed in detail with the original BLA submissions and resulted in a boxed warning for serious infections including tuberculosis. Additional warnings include gastrointestinal perforation, laboratory abnormalities, hypersensitivity reactions, including anaphylaxis, and the use of live vaccines.

9. Advisory Committee Meeting

This supplemental application is for an ancillary claim for an already approved indication; thus no Advisory Committee meeting was warranted.

10. Pediatrics

The pediatric issues were discussed in the reviews of the original BLAs.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**—No issues
- **Other GCP issues**—No issues
- **DSI audits** – The OSI audits were conducted as part of the original NDA
- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Proprietary name**

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

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments.**

None.

- **Physician labeling**

I recommend the following revisions (all to Section 14, Clinical Studies):

1) Proposed SF-36 labeling language:

- Consistent with the applicant's proposed text, describe SF-36 data under a separate subsection "Other Health Related Outcomes" to reflect the intended use of SF-36 as a general health status instrument and not only as supportive evidence of improvement in physical function.

- Revise the Applicant's proposed (b) (4) with general health status for consistency with the intended use of SF-36 instrument.
- Consistent with the applicant's proposed text, for completeness for SF-36 interpretation, include a description of physical component summary (PCS) and mental component summary (MCS) scores. This recommendation is consistent with standard practice in reporting SF-36 results because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores. Further, this approach is consistent with the analysis and reporting of composite endpoints, where the analyses and reporting of the individual components are descriptive without requiring statistical significance, i.e. adjusting for multiplicity.
- Delete the (b) (4) qualifier from the proposed statement. Inclusion in the product labeling implies (b) (4)

Proposed labeling revisions (deletions are in ~~strikethrough~~ and new text is in *red italic*):

14.1 Rheumatoid Arthritis-Intravenous Administration

“General health status (b) (4) was assessed by the Short Form Health Survey (SF-36) in Studies I-V. (b) (4) 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. (b) (4)

14.2 Rheumatoid Arthritis-Subcutaneous Administration

“General health status (b) (4) was assessed by the (b) (4) (SF-36) in Studies SC-I and SC-II. (b) (4) Patients receiving Actemra demonstrated greater improvement from baseline compared to placebo in the (b) (4) (PCS), (b) (4) (MCS), and in all 8 domains of the SF-36. (b) (4)

- 2) With these supplements, the Applicant submitted updates to the labeling to comply with the PLLR requirements.⁶ The proposed changes were reviewed by the Pharmacology and Toxicology review team and the consultants from Division of Pediatric and Maternal Health (DPMH). While the proposed structure was consistent with the PLLR requirements, revisions to the proposed labeling changes were made consistent with the recommendations from these teams based on the review of the available data from the submissions and from published literature. The Pharmacology and Toxicology review team also updated Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, based on data from the currently available published literature.

⁶ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf>

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

None.

- **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 with the original BLAs. No changes are proposed to the Patient labeling/Medication guide with this submission.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplement with revisions to the labeling as discussed in the section on Labeling above.

- **Risk Benefit Assessment**

The overall risk-benefit profile of tocilizumab in RA remains favorable, as determined at the time of the original BLA approvals and is not altered on the basis of this submission. The current submission supports the addition of SF-36 results in Section 14 of the prescribing information. Although the risks of tocilizumab are not minimal, these are balanced by a number of clinical benefits, which include reduction in patient's signs and symptoms and disease activity, improvement in physical functioning, and general health status.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

These supplements do not warrant new postmarketing risk evaluation and management strategies (REMS).

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

These supplements do not warrant new postmarketing requirements or commitments.

- **Recommended Comments to Applicant**

None.

Bibliography:

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- ^{vi} Kremer JM et al,, Ann Intern Med. 2002 Nov 5;137(9):726-33
- ^{vii} Maini RN et al, Arthritis Rheum. 2004 Apr;50(4):1051-65
- ^{viii} Strand V et al, Rheumatology (Oxford). 2012 Oct;51(10):1860-9

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/s/

NIKOLAY P NIKOLOV
09/22/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number	125276/107; 125472/18
Priority or Standard	Standard
Submit Date	November 24, 2015
Received Date	November 24, 2015
PDUFA Goal Date	September 24, 2016
Division / Office	DPARP/OND
Reviewer Name	Rachel L. Glaser, M.D.
Review Completion Date	August 3, 2016
Established Name	Tocilizumab
Trade Name	Actemra
Therapeutic Class	IL-6 inhibitor
Applicant	Hoffman-La Roche, Ltd
Formulation(s)	Intravenous (IV), subcutaneous (SC)
Dosing Regimen	IV: 4 mg/kg every 4 weeks, increase to 8 mg/kg every 4 weeks based on clinical response SC: Weight <100 kg: 162 mg every other week, increase to 162 mg weekly based on clinical response Weight ≥100 kg: 162 mg weekly
Indication	Rheumatoid Arthritis (RA), SF-36 claim
Intended Population	Moderate-to-Severe RA

Template Version: March 6, 2009

1. Introduction

Actemra[®] (tocilizumab), a monoclonal antibody directed against interleukin-6, was approved by the FDA under BLA 125276 on January 8, 2010 for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies, to be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs) at a starting dose of 4 mg/kg by intravenous infusion every 4 weeks followed by an increase to 8 mg/kg based on clinical response. Additional claims for inhibiting the progression of structural damage, inducing major clinical response, and improving physical function were subsequently added (January 4, 2011). On October 11, 2012, the indication was updated to the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. Actemra[®] (tocilizumab) is also approved for treatment of systemic juvenile idiopathic arthritis (JIA) and polyarticular JIA in patients 2 years of age and older (dates of approval April 15, 2011 and April 29, 2013, respectively). A subcutaneous formulation was approved for adult patients with rheumatoid arthritis on October 21, 2013 under BLA 125472. The initial dose for patients <100 kg weight is 162 mg subcutaneously every other week, followed by an increase to every week based on clinical response, while the starting dose is 162 mg SC weekly for those patients ≥100 kg.

This submission is a request for re-consideration for inclusion of Short Form 36 (SF-36) data in the product labeling for data submitted in the original BLA applications. It is being reviewed as efficacy supplements (BLA 125276/107; BLA 125472/18). Hoffman-La Roche proposes the following labeling changes in the Health Related Outcomes section of Section 14:

14.1 Rheumatoid Arthritis-Intravenous Administration

(b) (4)

14.2 Rheumatoid Arthritis-Subcutaneous Administration

(b) (4)

Historically, until 2005, SF-36 was included in the labeling for RA products, as supportive data for the Health Assessment Questionnaire Disability Index (HAQ-DI) for the claim of improvement in physical function. From 2006 through 2013, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) denied proposed labeling for SF-36 due to concerns raised by the Study Endpoints and Labeling Development (SEALD) team about the SF-36 instrument and in particular the use of the SF-36 physical component summary (PCS) score and mental component summary (MCS) score in RA product labels. SEALD maintained

that SF-36 was a generic health survey that has not been shown to represent a complete, meaningful, interpretable, and appropriate measure of health related quality of life specific for the RA, psoriatic arthritis, or ankylosing spondylitis. Continued pushback from the rheumatology academic community for DPARP and SEALD to reassess the SF-36 for re-implementation in RA product labels led to an internal Regulatory Briefing held September 20, 2013 to discuss the relevant regulatory history of SF-36 use in RA drug development and labeling. DPARP, with the support of CDER senior management, determined that SF-36 could be included in RA labeling as a measure of general health status, rather than its previous use as a supportive measure for improvement in physical function. Inclusion of results of PCS, MCS, and the results of the 8 domains facilitate interpretation of the SF-36. In November 2013, Xeljanz[®], another treatment for RA, was approved with inclusion of an SF-36 statement supportive of general health status. In August 2015, Simponi Aria[®] received a similar claim.

The overall development program was discussed in detail in the primary review of the original BLAs dated, August 1, 2008 (BLA 125276) and September 16, 2013 (BLA 125472). This document will focus on:

- Regulatory history of SF-36 in RA product labeling
- Analyses on the SF-36 data from the tocilizumab clinical development
- Updated labeling recommendations to include SF-36 results as a measure of general health status

The overall clinical efficacy and risk-benefit analysis of tocilizumab remain consistent with the original BLA applications. Further, the Agency's analyses of the SF-36 data are in general agreement with the sponsor's analyses. Thus the SF-36 data submitted are adequate to support inclusion in product labeling.

2. Background

Rheumatoid arthritis (RA) is a chronic symmetric inflammatory polyarthritis, affecting approximately 1% of the adult population worldwide. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system.¹ Thanks to the advances in our understanding of the disease and the established drug development pathway, many effective treatments have been developed and approved for RA. The approval of most of these products was supported by establishing efficacy in the key domains of the disease, namely clinical response and physical function based on internationally agreed upon endpoints. The clinical response has been assessed by ACR response rates¹ and measures of low disease activity, such as DAS28² less than 2.6, have been used as supportive evidence of efficacy in this domain. For

1 ACR20 (50, 70) response criteria — American College of Rheumatology response criteria is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50, 70) percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, physician global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index (HAQ-DI)), and acute phase reactants.

2 DAS28 — Disease Activity Score 28 is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis.

physical function, the Health Assessment Questionnaire Disability Index (HAQ-DI)³ is usually used to demonstrate an improvement in physical function, and the SF-36, and more specifically the Physical Component Summary (PCS) has been historically used as supportive evidence of efficacy in this domain. Other outcomes that have important implications for patients and health care providers, such as radiographic endpoints, have been used to provide further characterization of the efficacy of a drug product and its utility in clinical practice.

There has been a recent emphasis on studying the effects of treatments on aspects of the disease that are important to patients and are not captured by other outcomes.ⁱⁱ These measures include patient-reported outcomes (PROs) such as the generic SF-36 health survey, the subject of this supplemental application.

Relevant Regulatory History of SF-36 in Tocilizumab RA Development

SF-36 was collected as a patient-reported outcome of interest in the protocols of all phase 3 confirmatory clinical studies and submitted in the original BLA applications to support a labeling claim of improvement in physical functioning. At the time of the original BLA 125276 application, the Division denied including SF-36 data in the product labeling as the SF-36 was insufficient to support a claim of improvement in physical function without longer term data from the HAQ-DI. At the time of the submission of BLA 125472, the Division denied including SF-36 data in the product labeling citing concerns expressed by the SEALD team that SF-36 is not an optimal PRO for use to support physical function labeling claims, and that mental and physical component summary scores may not be sufficient to describe SF-36 results. This rationale is further discussed in the section Regulatory History of SF-36 in RA Drug Development below. The proposed language in the draft product label regarding SF-36 scores was removed during labeling discussions with the Division during the respective BLA review cycles.

Regulatory History of SF-36 in RA Drug Development

The purpose of this section is to discuss the regulatory history of SF-36 Health Survey in RA drug development and DPARP's justification for re-implementing SF-36 in RA product labeling as stand-alone results reflecting general health status. The history, development, use, and limitations of the SF-36 instrument are described in further detail in Section Clinical/Statistical - Efficacy below.

In the 1999 RA Guidance, the SF-36 was mentioned as a validated general health status measure that should be collected in trials intended to support a "prevention of disability" claim, and that patients should not worsen on this measure over the duration of the trial. This claim was intended to encourage long-term trials (i.e. 2 to 5 years) in RA. Over time, the language of the claim and data required evolved. The claim became "improvement in physical function" and the primary measure used throughout development programs became the Health Assessment Questionnaire Disability Index (HAQ-DI). Shorter trials were accepted as

³ HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

significant improvement could be observed within 12 to 24 weeks, and it became difficult to justify long-term placebo-controlled trials with the approval of highly effective therapies.

SF-36 was included in the labeling for RA products, as supportive data for the HAQ-DI for the claim of improvement in physical function. Between 1998 and 2005, six disease modifying antirheumatic drugs (DMARDs) were approved for the treatment of patients with RA with inclusion of the SF-36. In most of these labels, mention of SF-36 is limited to a descriptive statement that improvements in SF-36 PCS and MCS were observed. The last approved label with SF-36 during this period (abatacept/Orencia[®], 2005) contains the statement, “Health-related quality of life was assessed by the SF-36 questionnaire...improvement was observed in the Orencia[®] group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).” In 2006, rituximab (Rituxan) was approved for RA but was not given labeling for SF-36 because 2-year data were not submitted.

From 2008 through 2013, the Agency denied proposed labeling for SF-36 claims due to concerns raised by the SEALD team about the SF-36 instrument and, in particular, the use of the SF-36 PCS and MCS score in RA product labels. These concerns included (1) SF-36 is a generic health survey that has not been shown to represent a health related quality of life (HRQoL) in RA and (2) PCS, MCS are composite measures of weighted scores from all 8 subconcepts/domains, are not independent, and cannot be described in a way that is meaningful. After internal discussion, the review division reevaluated the need for SF-36 and determined that SF-36 was not needed to support the improvement in physical function claim. As a result, SF-36 information from four RA products, golimumab/Simponi[®], certolizumab/Cimzia[®], tocilizumab/Actemra[®], and tofacitinib/Xeljanz[®], was not included in the originally approved product labeling.

In addition to expected pushback from sponsors, who felt that this created an unfair disadvantage, the decision to no longer include SF-36 in RA product labeling was questioned by the RA academic and research community. The community’s rationale for the importance of SF-36 included: (1) SF-36 is a legacy instrument with well-known limitations and implications that is widely used by the RA research community throughout the world, (2) SF-36 provides additional important information on the impact of the disease on the patient that is not captured by other outcome measures used in RA trials, and (3) SF-36 is utilized throughout the world for health care policy and decision-making. The SF-36 has been extensively studied in the context of RA and other rheumatic diseases with a wealth of data across countries and cultures. The question about the content validity of the SF-36 in RA or other related rheumatic conditions, that the instrument does not measure what it is purported to measure, does not appear to be supported by the wealth of published literature on SF-36. It is ubiquitous in rheumatology and by far the most commonly used generic health status outcome in RA reported in over 150 articlesⁱⁱⁱ. It was used in 80% of the published clinical studies in RA reporting PROs^{iv} indicating that the community understands what SF-36, including the 8 domains and the summary scores, measure. Studies to date have yielded evidence of content, construct, and predictive validity of SF-36. Further, a systematic review of the literature on the measurement properties of physical function scales for use in patients with RA, has identified the SF-36 as a relevant generic questionnaire with respect to content validity for measuring

physical functioning^v, supported by the fact that, in RA, SF-36 PCS is well correlated with HAQ-DI.

Based on the accumulated clinical data and the evidence of construct validity, responsiveness, and reliability in RA, SF-36 has been shown to:

- Assess disease aspects important to patients
- Provide a multidimensional view of the impact of RA and improvements associated with effective treatment^{vi}
- Be a sensitive instrument to demonstrate treatment-associated changes in RA across populations with different demographic and disease characteristics
- Offer comparison with age- and gender matched norms and with other disease states and co-morbidities^{vii}
- Be non-redundant with other endpoints^{viii, ix}
- Reflects impact of early and later disease^{x, xi}
- Have generally accepted Minimal Clinically Important Difference (MCID) values for improvement as well as deterioration^{xii, xiii}

An internal Regulatory Briefing meeting was held September 20, 2013 and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), with support of CDER senior management, decided to implement SF-36 in RA labeling as a measure of general health status, rather than its previous use as a supportive measure for improvement in physical function. Inclusion of results of PCS, MCS, and the results of the 8 domains are included to facilitate interpretation. In November 2013, Xeljanz[®] (tofacitinib) was the first RA treatment since 2005 to receive approval for inclusion of an SF-36 claim in the labeling. Simponi Aria[®] (golimumab) subsequently received approval for an SF-36 claim in August 2015.

3. CMC/Device

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. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology 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.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology 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.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Overview of the Clinical Program

Five randomized placebo-controlled trials have been submitted as the primary evidence of efficacy and safety of IV tocilizumab and two randomized placebo-controlled trials have been submitted in support of SC tocilizumab, as summarized in Table 1 and Table 2 below.

Table 1: Key Design Features of the Pivotal IV Tocilizumab RA Studies

Study	Design/ Duration	Population/N	Dose Regimen	Primary Endpoint
WA17822	R, DB, PC 24 wk	Moderate to severe active RA in MTX-IR 623	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): TCZ 8 mg/kg	ACR20 at Wk 24
WA17823	R, DB, PC 52 wk	Moderate to severe active RA in MTX-IR 1196	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): Blinded TCZ 4 mg/kg (from PBO) or TCZ 8 mg/kg (from 4 mg/kg) After Wk 24: TCZ 8 mg/kg	ACR20 at Wk 24
WA17824	R, DB, DD, PC 24 wk	Active RA in MTX naïve or MTX discontinued 673	TCZ 8 mg/kg IV q4 wks + PBO PO /wk PBO IV q4 wks + MTX PO 7.5-20 mg/wk Substudy: PBO for 8 wks, then TCZ 8 mg/kg IV q4 wks for 16 wks Escape (Substudy, up to Wk 8): TCZ 8 mg/kg	ACR20 at Wk 24
WA18062	R, DB, PC 24 wk	Moderate to severe active RA in TNF-IR 499	TCZ 4 mg/kg IV q4 wks + MTX 10-25 mg/wk TCZ 8 mg/kg IV q4wks + MTX 10-25 mg/wk PBO IV q4 wks + MTX 10-25 mg/wk Escape (Wk 16): TCZ 8 mg/kg	ACR20 at Wk 24
WA18063	R, DB, PC 24 wk	Moderate to severe active RA in DMARD-IR 1220	TCZ 8 mg/kg IV q4wks + standard DMARDs PBO IV q4 wks + standard DMARDs Escape (Wk 16): Adjustment of background DMARDs	ACR20 at Wk 24

DB=double blind, R = randomized, PC = placebo controlled, DD = double dummy, OL = open label, IR = inadequate responders, TCZ = tocilizumab, MTX = methotrexate, PBO = placebo

Source: Adapted from BLA 125276 Module 2.7.3 Summary of Efficacy Tables 1, 4

Phase 3 Confirmatory Studies IV Tocilizumab Studies in RA

Study WA17822 was a 24 week randomized, double-blind, placebo-controlled study in 623 patients with moderately to severely active RA with previous inadequate clinical response to MTX at a dose of 10-25 mg per week. Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks. All patients received background treatment with a stable dose of MTX 10 to 25 mg weekly. Concomitant NSAIDs and corticosteroids (≤ 10 mg/day prednisone equivalent) at stable doses were permitted. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at Week 16 were eligible for escape therapy (TCZ 8 mg/kg + MTX) at Weeks 16 and 20. The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the Week 24 visit, all patients (including escape patients) could enter an open-label long-term extension study (WA18695) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years. SF-36, a secondary efficacy and a quality of life endpoint, was systematically collected per protocol at baseline, Week 8, Week 16, and Week 24. Those patients that received escape treatment had SF-36 assessed at Weeks 20 and 24.

Study WA17823 was a 104 week (52 week double-blind followed by 52 week open-label, with optional 3-year extension phase) randomized, double-blind, placebo-controlled study in 1196 patients with moderately to severely active RA with previous inadequate clinical response to MTX at a dose of 10-25 mg per week. Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks. All patients received background treatment with a stable dose of MTX 10 to 25 mg weekly. Concomitant NSAIDs and corticosteroids (≤ 10 mg/day prednisone equivalent) at stable doses were permitted. After Week 24, patients who achieved a $\geq 50\%$ improvement in both SJC and TJC at 2 consecutive visits were permitted a dose reduction in NSAIDs according to the investigator's normal practice. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at Week 16 (and through Week 48) were eligible for escape therapy. Patients who were initially assigned to receive TCZ 4 mg/kg or 8 mg/kg were assigned to receive TCZ 8 mg/kg as escape therapy; patients initially assigned to receive placebo, received TCZ 8 mg/kg as escape therapy. If after 3 doses or more of escape therapy, patients continued to show less than 20% improvement from baseline in both SJC and TJC, they would receive open-label treatment with TCZ 8 mg/kg. The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. SF-36, a secondary efficacy and a quality of life endpoint, was systematically collected per protocol at baseline, and Weeks 8, 16, 24, 32, 40, 52, and 104 and was included in the statistical hierarchy of endpoints.

Study WA17824 was a 24 week randomized, double-blind, parallel group, non-inferiority study in 673 patients with moderately to severely active RA who had not been treated with MTX within 6 months prior to randomization, and who had not discontinued previous MTX treatment due to toxicity or lack of response. Patients were randomized (1:1) to receive either TCZ 8 mg/kg IV every 4 weeks plus placebo MTX capsules or MTX oral capsules weekly plus placebo IV infusion every 4 weeks. MTX was provided in an escalating dose regimen starting at 7.5 mg weekly, increasing to 15 mg weekly at Week 4 if the patient had any swollen

or tender joints, then to 20 mg weekly at Week 8 if the patient had joint activity. Concomitant NSAIDs and corticosteroids (≤ 10 mg/day prednisone equivalent) at stable doses were permitted throughout the study. As an internal control for efficacy, some patients at centers in Canada, Israel, and the United States were enrolled into a placebo-controlled substudy in which they would receive 8 weeks total of placebo capsules and placebo IV infusions. At Week 8, patients received TCZ 8 mg/kg plus placebo MTX capsules for the remaining 16 weeks of the study. Only patients in this placebo-controlled substudy were eligible for escape therapy (to open-label TCZ 8 mg/kg IV) if they experienced a 20% increase in the number of active swollen and tender joints at any of the first 7 weekly visits. The primary efficacy analysis, performed on the per-protocol population, was a non-inferiority comparison (pre-specified non-inferiority margin of 12%) of the proportion of ACR20 responders at Week 24 in the MTX group versus the TCZ 8 mg/kg group. If TCZ was shown to be non-inferior to MTX in ACR20 response at Week 24, testing for superiority was pre-specified. SF-36, a secondary efficacy and a quality of life endpoint, was systematically collected at baseline, Week 8, Week 16, and Week 24.

After completion of 24 weeks of randomized treatment, patients could continue double blind treatment in a “Transition Phase” or enter an open-label, long-term extension study (WA18696) in which they received TCZ 8 mg/kg every 4 weeks for up to 5 years. Patients who achieved a $\geq 50\%$ decrease in the number of active swollen and tender joints (compared to baseline) while receiving their current blinded study treatment at both Week 20 and Week 24 had the option of continuing their current blinded study treatment until the last patient enrolled in the study and the study database was locked. Patients not maintaining this level of improvement could immediately enroll in WA18696 and receive open-label TCZ treatment.

Study WA18062 was a 24 week randomized, double-blind, placebo-controlled study in 499 patients with moderately to severely active RA with previous inadequate clinical response to, or who were intolerant of, treatment with one or more TNF inhibitor therapies within one year prior to randomization. Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks. All patients received background treatment with a stable dose of MTX 10 to 25 mg weekly. Concomitant NSAIDs and corticosteroids (≤ 10 mg/day prednisone equivalent) at stable doses were permitted throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at Week 16 were eligible for escape therapy (TCZ 8 mg/kg + MTX) at Weeks 16 and 20. The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the Week 24 visit, all patients (including escape patients) could enter an open-label long-term extension study (WA18696) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years. SF-36, a secondary efficacy and a quality of life endpoint, was systematically collected per protocol at baseline, Week 8, Week 16, and Week 24.

Study WA18063 was a 24 week randomized, double-blind, placebo-controlled study in 1220 patients with moderately to severely active RA with previous inadequate clinical response to non-biologic DMARDs, including MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide. Patients were randomized (2:1) to receive TCZ 8

mg/kg IV every 4 weeks or placebo IV every 4 weeks, in addition to background treatment with their current DMARD(s). Concomitant NSAIDs and corticosteroids (≤ 10 mg/day prednisone equivalent) at stable doses were permitted throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at Week 16 were eligible for escape therapy (adjustment of the background DMARD dose and/or treatment with a different traditional DMARD, increase in corticosteroid dose up to 10 mg/day, or intraarticular corticosteroids) at Weeks 16 and 20. The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the Week 24 visit, all patients (including escape patients) could enter an open-label long-term extension study (WA18696) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years. SF-36, a secondary efficacy and a quality of life endpoint, was systematically collected per protocol at baseline, Week 8, Week 16, and Week 24.

Table 2: Key Design Features of the Pivotal SC Tocilizumab RA Studies

Study	Design/ Duration	Population/N	Dose Regimen	Primary Endpoint
WA22762	24 wk, R, DB, DD, AC, PG	Moderate to severe active RA in DMARD/ bDMARD-IR 1262	TCZ 162 mg SC qwk + PBO IV q4 wks + DMARD PBO SC qwk + TCZ 8 mg/kg IV q4wks + DMARD	ACR20 at Wk24
NA25220	24 wk, R, DB, PC	Moderate to severe active RA in DMARD/ bDMARD-IR 656	TCZ 162 mg q2wk + DMARD PBO SC q2wk + DMARD Escape (Wk 12-24): TCZ 162 mg SC qwk	ACR20 at Wk24

DB=double blind, R = randomized, PC = placebo controlled, DD = double dummy, AC= active controlled, PG= parallel group, IR = inadequate responders, DMARD = disease modifying anti-rheumatic drug, TCZ = tocilizumab, PBO = placebo

Source: Adapted from BLA 125472 Module 2.7.3 Summary of Efficacy Table 1

Phase 3 Confirmatory Studies SC Tocilizumab Studies in RA

Study WA22762 was a 24 week randomized, double-blind, double-dummy, active-controlled, parallel group study in 1262 patients with moderately to severely active RA with previous inadequate clinical response to DMARD therapy, that included one or more anti-TNF biologic agents. TNF-inadequate responders were limited to 20% of the patients. Patients were randomized (1:1) to receive TCZ 162 mg SC weekly with placebo IV q4 weeks or to receive placebo SC weekly with TCZ IV 8 mg/kg q4 weeks, in addition to background DMARD therapy. Concomitant NSAIDs and corticosteroids (≤ 10 mg/day prednisone equivalent) at stable doses were permitted throughout the study. The primary endpoint was the difference in the proportion of ACR20 responders at Week 24. After completion of the Week 24 visit, all patients could be re-randomized to receive either TCZ 162 mg SC qw or TCZ 8 mg/kg IV q4

weeks for a 72 week open-label extension period. Patients originally randomized to SC TCZ were re-randomized in 11:1 ratio, while those originally receiving IV TCZ were re-randomized in a 1:2 ratio. SF-36, a quality of life endpoint, was systematically collected per protocol at baseline, Week 12, and Week 24.

Study NA25220 was a 24 week, randomized, double-blind, parallel group study in 656 patients with moderately to severely active rheumatoid arthritis with an inadequate response to DMARDs that may include one or more anti-TNF biologic agents. TNF-inadequate responders were limited to 20% of the patients. Patients were randomized (2:1) to receive TCZ 162 mg SC q2 weeks via prefilled syringe or placebo, in addition to background DMARD therapy. From Weeks 12 to 48, patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) were eligible for escape therapy (TCZ 162 mg SC qwk). Patients who received escape therapy could continue open-label treatment until the completion of the trial. The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. At Week 24, all patients, excluding those who escaped, were re-randomized to receive TCZ 162 mg SC q2wk via autoinjector or pre-filled syringe for a 72 week open-label extension period. SF-36, a secondary efficacy endpoint, was systematically collected per protocol at baseline, Week 12, and Week 24 during the double-blind period, and Week 48, Week 96, and Withdrawal in the open-label period.

Key eligibility criteria

Key eligibility criteria for enrollment in the Pivotal IV studies were:

- Men and women 18 years of age or greater who had been diagnosed with rheumatoid arthritis (RA) by ACR criteria
 - Disease duration ≥ 6 months (except for Study WA17824 that included patients with a disease duration ≥ 3 months)
 - Active RA as manifested by ≥ 6 out of 66 swollen and ≥ 8 out of 68 tender/painful joints and an elevated acute phase reactant test (CRP ≥ 1 mg/dL and/or ESR ≥ 28 mm/h)
 - In WA17823, patients had to have radiographic evidence of RA with at least one joint with a definite erosion
- Previous DMARD therapy and response eligibility criteria:
 - In WA17822, WA17823, and WA18062, patients must have had an inadequate therapeutic response to MTX; while in WA18063 patients must have had an inadequate response to a non-biologic DMARD
 - In WA17824, patients were MTX naïve or had not received MTX within 6 months of randomization and did not discontinue MTX as a result of clinically important toxic effects or lack of response
 - In WA18062, patients must have had an inadequate response to at least one TNF inhibitor within one year prior to randomization
- Concomitant medications:
 - Patients continued their stable dose of MTX in Studies WA17822, WA17823, and WA18062 or permitted DMARD in WA18063

- Oral corticosteroids (≤ 10 mg prednisone or equivalent) and NSAIDs (up to maximum recommended dose) were permitted if on stable doses for ≥ 6 weeks prior to baseline
- Appropriate contraceptive measures were required for men and women of childbearing potential
- Exclusion criteria:
 - Functional class IV (ACR Classification of Functional Status in RA)
 - Intra-articular or parenteral corticosteroids within 4 weeks
 - Autoimmune rheumatic diseases other than rheumatoid arthritis and secondary Sjögren's Syndrome
 - Unsuccessful treatment with an anti-TNF agent, except in Study WA18062
- Pregnant and nursing women were excluded. Other exclusions were: serious, chronic or current infections, including tuberculosis, herpes zoster, hepatitis B or C; recent receipt of a live virus vaccine; a history of or active immunodeficiency; evidence of or history of malignancy within 10 years (or breast cancer within 20 years); history of diverticulitis or other symptomatic lower GI conditions that might predispose to perforations; previous treatment with cell-depleting therapies; uncontrolled medical conditions; baseline clinically significant abnormalities in safety laboratory tests including hemoglobin, leukocyte, neutrophil, lymphocyte and platelet counts, hepatic transaminases or total bilirubin, serum creatinine; body weight > 150 kg; and recent history of alcohol or drug abuse

Key eligibility criteria for enrollment in the Pivotal SC studies were:

- Men and women 18 years of age or greater who had been diagnosed with RA
 - Disease duration ≥ 6 months
 - Active RA as manifested by ≥ 4 out of 66 swollen and ≥ 4 out of 68 tender/painful joints (Study WA22762) or by ≥ 6 out of 66 swollen and ≥ 8 out of 68 tender/painful joints (Study NA25220) and an elevated acute phase reactant test (CRP ≥ 1 mg/dL and/or ESR ≥ 28 mm/h).
 - In Study NA25220, patients had radiographic evidence of at least one joint with a definite erosion attributable to RA
- Patients must have had an inadequate response to DMARD therapy. DMARD therapy may include one or more TNF-inhibitors
- Concomitant medications:
 - Permitted DMARD(s) on stable dose for ≥ 8 weeks prior to baseline
 - Oral corticosteroids (≤ 10 mg prednisone or equivalent) and NSAIDs (up to maximum recommended dose) permitted if on stable doses ≥ 4 weeks prior to baseline
- Appropriate contraceptive measures were required for men and women of childbearing potential
- Exclusion criteria:
 - Functional class IV (ACR Classification of Functional Status in RA)
 - Intra-articular or parenteral corticosteroids within 4 weeks
 - Autoimmune rheumatic diseases other than rheumatoid arthritis and secondary Sjögren's Syndrome

- Pregnant and nursing women were excluded. Other exclusions were: serious, chronic or current infections, including tuberculosis, herpes zoster, hepatitis B or C; recent receipt of a live virus vaccine; a history of or active immunodeficiency; evidence of or history of malignancy within 10 years (or breast cancer within 20 years); history of diverticulitis or other symptomatic lower GI conditions that might predispose to perforations; previous treatment with cell-depleting therapies; uncontrolled medical conditions; baseline clinically significant abnormalities in safety laboratory tests including hemoglobin, leukocyte, neutrophil, lymphocyte and platelet counts, hepatic transaminases or total bilirubin, serum creatinine; body weight > 150 kg; and recent history of alcohol or drug abuse

Endpoints in Phase 3 RA Development Program

Treatment with IV and SC tocilizumab was shown to effectively reduce signs and symptoms of active arthritis as measured by ACR 20 response rate at Week 24 as the primary endpoint. Secondary endpoints in the IV program included ACR 50 and 70 responses, changes from baseline in individual parameters of the ACR core set, change in DAS28, DAS28 remission, EULAR response, change in hemoglobin, ACRn, HAQ, and other measures. Secondary endpoints in the SC program included ACR 50 and 70 responses, DAS28 remission, and proportion of patients with decrease in HAQ-DI ≥ 0.3 . In addition, inhibition of progression of radiographic changes was evaluated in Study WA17823 and Study NA25220.

SF-36 PCS and MCS summary scores were secondary endpoints and quality of life endpoints in the IV TCZ studies WA17822, WA17823, WA17824, WA18062, and WA18063, and SC TCZ Study NA25220, while these measures were considered quality of life endpoints and exploratory endpoints in SC TCZ Study WA25220. Results of SF-36 are discussed in detail below. Detailed protocol design, study conduct and results of endpoints such as ACR responses and HAQ-DI for individual studies are discussed in the original BLA applications and will not be discussed in this review.

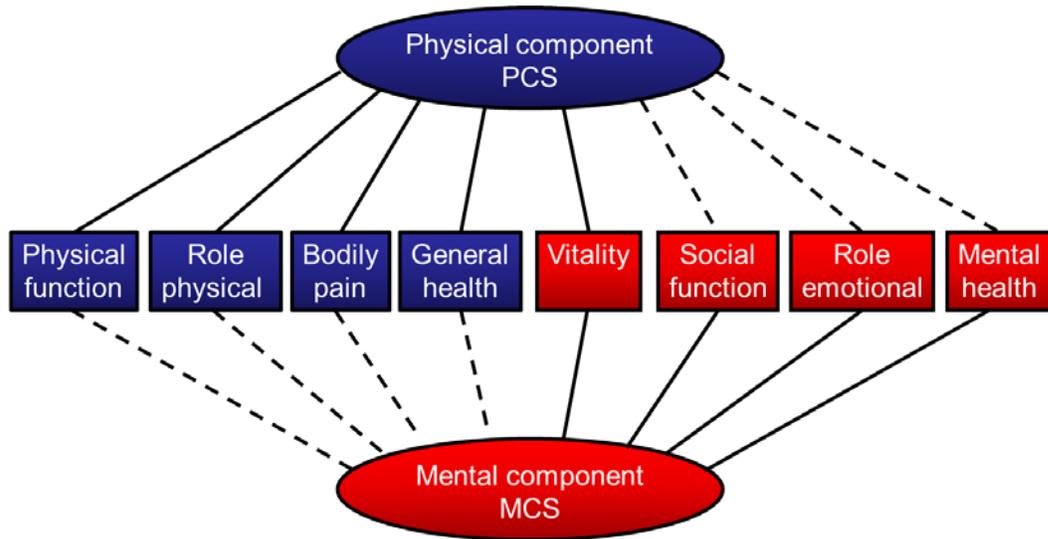
Brief Description of Short Form 36 (SF-36) Instrument

The SF-36 is a multi-purpose, short-form health survey. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. The SF-36 consists of 36 questions relating to either physical or mental health. One question asks respondents to rate the amount of change experienced in their health in general and the remaining 35 questions are divided into eight domains: four for physical health (physical health, bodily pain, physical functioning and physical role limitations) and four for mental health (mental health, vitality, social functioning and emotional role limitation). The eight domains are age, and gender adjusted and scored 0 (severe impairment) – 100 (no impairment).

Subsequently, two psychometrically-based summary measures, physical component summary (PCS) and mental component summary (MCS), were developed to simplify the analysis and interpretation of the SF-36. PCS measures how decrements in physical function affect day to day activities and MCS measures the impact of mental affect and symptoms of pain on quality

of life. The PCS and MCS are reported based on normative-based scoring. The conceptual model to derive the two summary scores is presented in Figure 1, where the solid lines identify a major positive contribution to the summary score and the dashed lines indicate a negative contribution.

Figure 1. Conceptual Model for Deriving PCS and MCS from the Individual Domains



Several issues with the component scores have been raised by the SF-36 scientific community:

- Interpretation: There are issues with the interpretation of the summary scores (PCS and MCS) because both summary scores are calculated as a weighted sum of all eight subscale scores rather than the weighted sum of the four scales hypothesized in the measurement model (i.e., PCS consisting of PF, RP, BP, and GH; MCS consisting of VT, SF, RE, and MH).
- Many articles by measurement experts have voiced concern that the component scores do not adequately summarize the eight subscale scores.^{xiv, xv}
- Multiple cases have been published where the change in component scores and the change in subscale scores have been inconsistent. Usually the inconsistencies occur in cases where there is a large effect in a domain subscale with a substantial negative factor coefficient.
- The method used by the developers forced the PCS and MCS to be uncorrelated. Several authors have stated that is unrealistic and is one of the causes for the negative factor scores coefficients. They proposed an alternative method that allows the PCS and MCS to be correlated. However, the developers respond that the alternative method is more difficult to interpret and there are still some negative factor score coefficients although they are smaller in absolute value than the case that assumes the PCS and MCS are uncorrelated.^{xvi}
- Several authors have shown for several different populations that the best fitting model is one that computes the component scores using only the four subscales they were hypothesized to include.
- Acceptability of the factor score coefficients

Because the factor score coefficients were derived from a sample of the U.S. general population, it is imperative to assess whether this sample has the same factor structure for the eight domain subscales as the RA patient population. Several authors have provided evidence that the factor structure was similar between the U.S. general population and the RA patient population.

Importantly, based on the above considerations and because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores, the SF-36 researchers have consistently emphasized the need to interpret the results of the domains, and PCS and MCS in parallel. Minimal clinically important difference (MCID) of 2.5-5 points for the composite scores and 5-10 points for the domain scores have been proposed in the literature.^{xvii}

SF-36 in Tocilizumab Development Program

Statistical Analysis of SF-36 Data

Thirty six-item Short Form Health Survey data was collected and analyzed for randomized subjects at the time points discussed above under “Overview of the Clinical Program”. In the intravenous tocilizumab program, changes from baseline in the PCS and MCS scores of SF-36 were summarized by treatment group and compared between groups using an ANOVA model with the stratification factor(s) applied at randomization. Stratification was by site in all studies; and in addition, study WA17824 was stratified by disease duration (≤ 2 years or > 2 years). Analyses of SF-36 for non-inferiority study 18724 included patients in the per-protocol population, defined as those patients who met inclusion criteria on the case report forms and remained on randomized treatment without rescue medication or protocol violations. Analyses of other studies included the intent to treat population, defined as all randomized patients who received at least one dose of study medication. A two-sided 5% significance level was used.

In studies WA17822, WA17823, and WA18062 which have two tocilizumab treatment groups and a control group, a sequential testing procedure was adopted such that the TCZ 8 mg/kg arm was compared to the control arm. If the derived p-value ≤ 0.05 , a comparison between the TCZ 4 mg/kg arm and the control arm was conducted. For study WA18063, a comparison of the TCZ treatment arm with the control arm was conducted. For study WA17824, a noninferiority study, a 95% confidence interval for the difference between means for all treatment comparisons was determined. If the lower limit of the 95% confidence interval for the treatment difference is >0 , then superiority was achieved.

To control for multiplicity, secondary efficacy parameters, including SF-36 PCS and MCS at 24 weeks, were hierarchically ordered and tested in a pre-defined sequential order. Summary statistics were reported for the composite scores and each of the 8 domains at baseline, and at Weeks 8, 16, and 24. In addition, summary statistics of change from baseline for the composite scores (at Weeks 8, 16, and 24) and each of the domains (at Week 24) were tabulated.

In the subcutaneous tocilizumab program, mean change from baseline to Week 24 in SF-36 PCS and MCS scores was a key secondary endpoint in study NA25220 and a key exploratory endpoint in study WA22762. In study NA25220, change from baseline in PCS and MCS were analyzed by ANCOVA on the intent to treat population adjusting for the stratification factors applied at randomization (region and weight category) and baseline value for comparisons between treatment arms. To control for multiplicity, secondary efficacy parameters, including SF-36 PCS and MCS at 24 weeks, were tested via a fixed sequence approach in study NA25220. Change from baseline in PCS and MCS at each visit were summarized descriptively for the per protocol population.

Handling of SF-36 Missing Data

For partially answered questionnaires, if more than 50% of the items within each domain were unanswered, the domain score would be assigned to missing and only observed values, including data collected after patient escape or withdrawal from randomized treatment, were used in the analyses. If at least 50% of the items within each domain were answered, the missing item scores were imputed with the average score across the completed items in the same scale. Aggregated scores were computed after the imputation rule was applied to the component domains, but set to missing if any domain was missing. Patients with missing aggregate scores were excluded from analyses and summary statistics. If a subject met the early escape criteria, the data collected at the escape visit was used as is and the SF-36 score was set to missing subsequently; no imputations of missing data were conducted. A sensitivity analysis utilizing a last observation carried forward method was conducted.

Patient Disposition

The population in the tocilizumab RA development program consisted of adult patients with moderate-to-severely active RA who had an inadequate response to methotrexate (studies WA17822, WA17823), one or more DMARDs (studies WA18063, WA22762, NA25220), one or more TNF inhibitors (study WA18062), or in study WA18724, patients who were naïve or had discontinued prior methotrexate therapy for reasons not related to toxicity or lack of efficacy. For further discussion on the patients' disease and demographic characteristics and disposition the reader is referred to the review of the original BLA applications.

Errors due to inadequate translations were noted in patient-reported questionnaires, including the SF-36, released to the study sites. Patients who received these questionnaires continued to complete the incorrect questionnaires, while newly enrolled patients completed the corrected questionnaires. A consultant at the International Quality of Life Assessment project assessed the errors in the SF-36 questionnaires and, based on the recommendations provided, questionnaires from Hungarian sites (WA17822) and Italian sites (WA17822) were excluded from the analysis. The excluded questionnaires from Hungarian sites were from 12 patients in the placebo + MTX group, 11 patients in the TCZ 4 mg/kg + MTX group, and 9 patients in the 8 mg/kg + MTX group. Questions 4 and 5 were excluded from the analysis in an additional 12 patients (3 patients in placebo + MTX, 6 patients in TCZ 4 mg/kg + MTX, and 3 patients in TCZ 8 mg/kg + MTX groups) from sites in Italy. In WA17824, < 10 enrolled patients completed incorrect questionnaires. In WA18063, one patient from a site in the USA had all

baseline, week 2, and week 4 SF-36 data excluded from the analysis; all other patient data from WA18063 was included in the analysis. All other errors were felt to be minor and the data was included in the analysis.

Results of SF-36 Data

IV Studies

At Week 24, all five IV tocilizumab studies showed significant differences between tocilizumab and placebo for changes from baseline in SF-36 physical component score (PCS) score (Table 3). Trends towards improvement in change from baseline in SF-36 mental component score (MCS) score were observed, however these did not reach statistical significance in Studies WA17823, WA17824, and WA18062. Responses in the placebo group at Week 24 may be overestimated due to patients who received escape therapy at Week 16. Studies WA17823, WA17824, and WA18062 had higher proportions of patients who received rescue therapy (33%, 38%, and 41% respectively), as compared to Studies WA17824 and WA18063 (4% and 11%, respectively). The improvements in PCS were observed in studies WA17824 and WA18063 in which fewer patients received rescue therapy, while those studies with higher proportions of patients who received rescue therapy failed to show statistically significant differences in change in MCS, suggesting that the proportion of patients receiving rescue therapy did not alter the conclusions of the assessment at Week 24. Overall, the PCS and MCS responses suggest a small incremental dose-response between tocilizumab 4 mg/kg and 8 mg/kg IV q 4 weeks regimens, consistent with the overall treatment benefit observed in the primary efficacy endpoints, as discussed in the original BLA application.

Table 3: Adjusted Mean Change in PCS and MCS scores by IV treatment group at Week 24

Study	SF-36 Measure	PBO + MTX/DMARD	TCZ 4 mg/kg + MTX/DMARD	TCZ 8 mg/kg + MTX/DMARD
WA17822	PCS	5.0	9.7*	9.5*
	MCS	2.7	5.7*	7.3*
WA17823	PCS	5.56	7.84*	8.15*
	MCS	2.84	3.23	4.18
WA17824	PCS	7.77	n/a	9.78**
	MCS	4.81	n/a	6.77
WA18062	PCS	2.22	7.09*	8.02*
	MCS	4.07	4.46	4.06
WA18063	PCS	4.08	n/a	8.87*
	MCS	2.26	n/a	5.31*

*p < 0.05

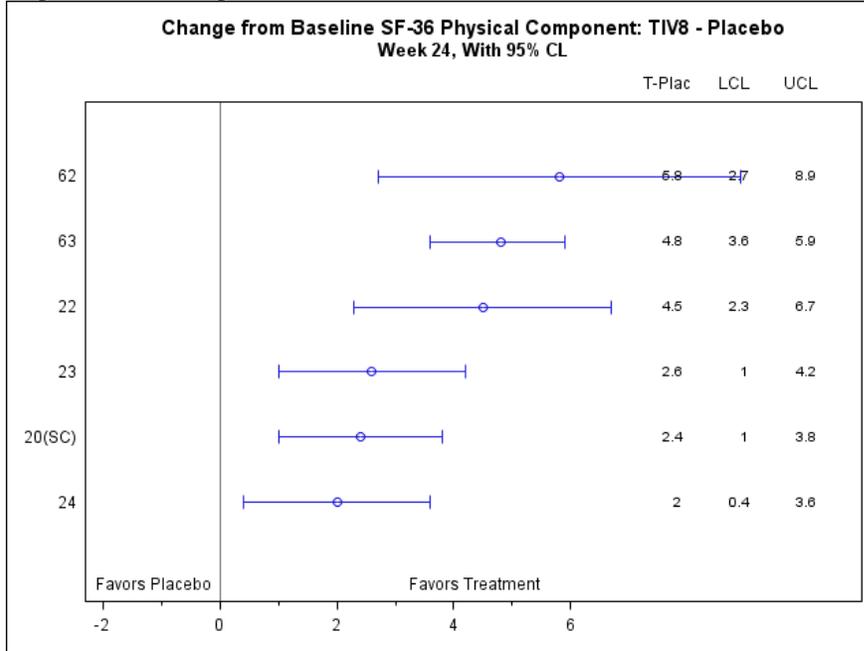
**For Study 18724, lower bound of 95% CI > 0

Source: Adapted from Applicant submission BLA 125276, CSR from Studies WA17822, WA17823, WA17824, WA18062, WA18063

Forest plot analyses performed by FDA Biostatistician Dr. Robert Abugov summarize the change in SF-36 scores by study. Comparison of the change from baseline in SF-36 PCS score

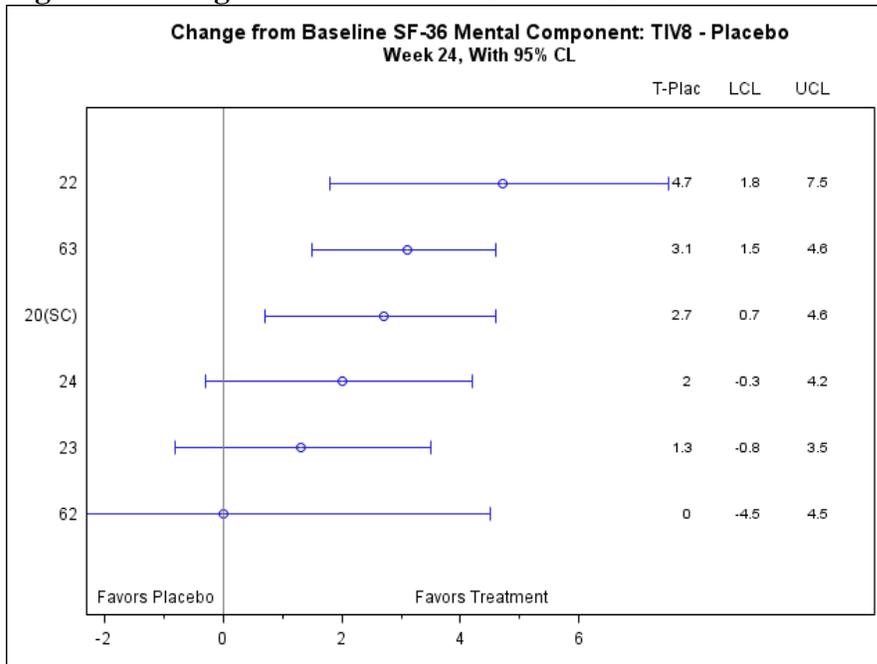
in the TCZ 8 mg/kg treatment groups as compared to placebo favors the TCZ treatment group in all IV studies, as well as the SC study NA25220 as show in Figure 2. Analysis of the treatment differences in change in SF-36 MCS scores shows a trend to greater improvement in MCS in the TCZ groups for all studies, except WA18062 as displayed in Figure 3. Similar findings are observed when the analysis is conducted with TCZ 4 mg/kg treatment groups for those studies that included this dose group. In addition, analysis of the 8 domains nominally favored treatment with TCZ 8 mg/kg over placebo in each study and favored treatment with TCZ 4 mg/kg over placebo for each domain except the social function domain for Study WA18723.

Figure 2: Change from Baseline in SF-36 PCS score at Week 24, by Study



8 mg/kg dose included in analysis for studies of IV tocilizumab
 Source: Analysis by FDA Statistical Reviewer Dr. Robert Abugov

Figure 3: Change from Baseline in SF-36 MCS score at Week 24, by Study

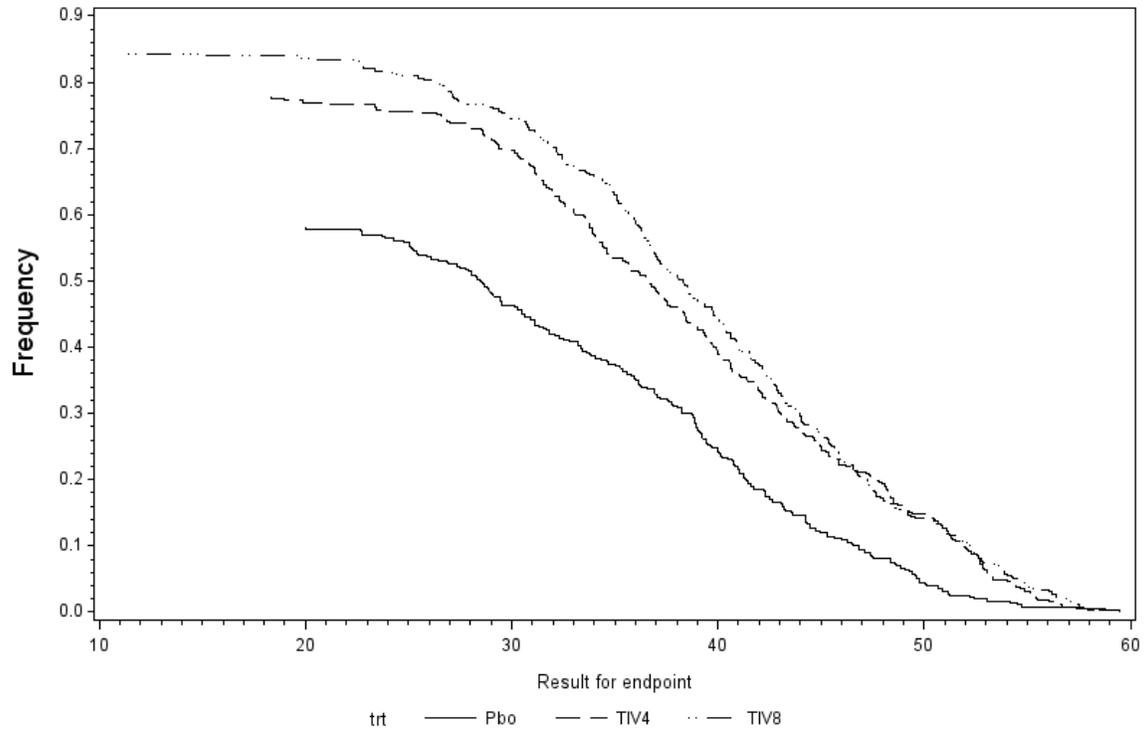


8 mg/kg dose included in analysis for studies of IV tocilizumab
 Source: Analysis by FDA Statistical Reviewer Dr. Robert Abugov

Sensitivity analyses, conducted by Dr. Abugov examined the continuous responder functions between placebo and treatment showed consistent results with the analyses of the mean change from baseline with clear separation between the tocilizumab and placebo groups, as shown in Figure 4 as representative of SF-36 PCS data from Study WA17823 and in Figure 5 as representative of SF-36 MCS data from Study WA17823.

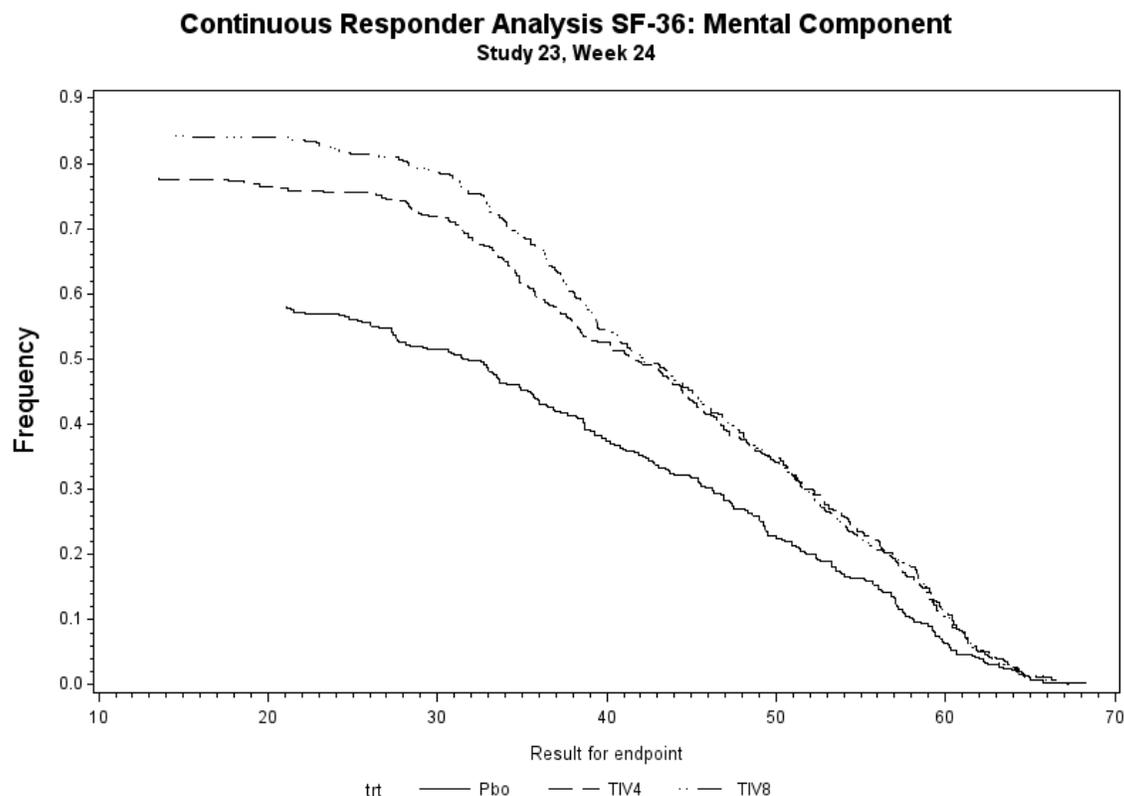
Figure 4: Change from Baseline SF-36 PCS score, Week 24, Study WA17823, Continuous Responder Analysis

Continuous Responder Analysis SF-36: Physical Component
Study 23, Week 24



Kolmogorov-Smirnov Test TIV8 vs Placebo: P-Value = 0.0290
Source: Analysis by FDA Statistical Reviewer Dr. Robert Abugov

Figure 5: Change from Baseline SF-36 MCS score, Week 24, Study WA17823, Continuous Responder Analysis



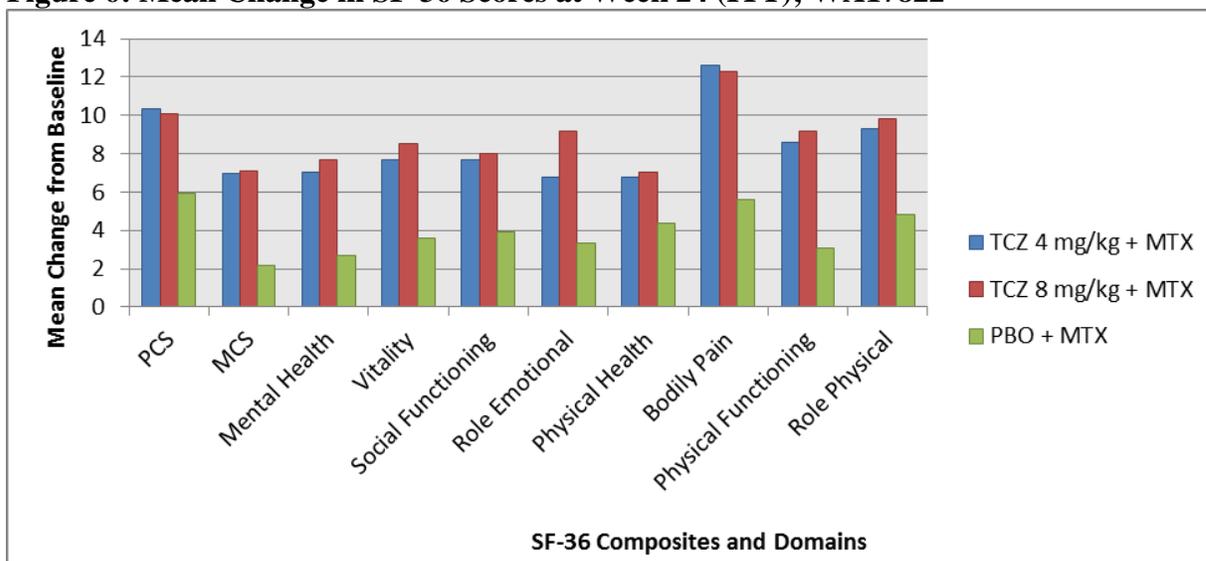
Kolmogorov-Smirnov Test TIV8 vs Placebo: P-Value = 0.8710
Source: Analysis by FDA Statistical Reviewer Dr. Robert Abugov

As noted above, minimal clinically important difference (MCID) of 2.5-5 points for the composite scores and 5-10 points for the domain scores have been proposed in the literature.
xvii

Study WA17822

Mean changes from baseline in PCS that exceeded the MCID were observed by Week 8 in both tocilizumab dose groups and were maintained until Week 24. A clinically relevant improvement in MCS was observed only in the TCZ 8 mg/kg + MTX group at Week 24. Clinically relevant improvements in PCS and MCS were not seen in the placebo + MTX group at any timepoint. Improvements were seen across the 8 domains with greater mean improvements in the TCZ + MTX groups compared with the placebo + MTX group as shown in Figure 6. Improvements in domain scores in the TCZ + MTX groups exceeded the MCID for all domains, while smaller improvements were observed in the placebo + MTX group.

Figure 6: Mean Change in SF-36 Scores at Week 24 (ITT); WA17822



Source: Adapted from Applicant submission, CSR WA17822; Tables 40, 41, 44

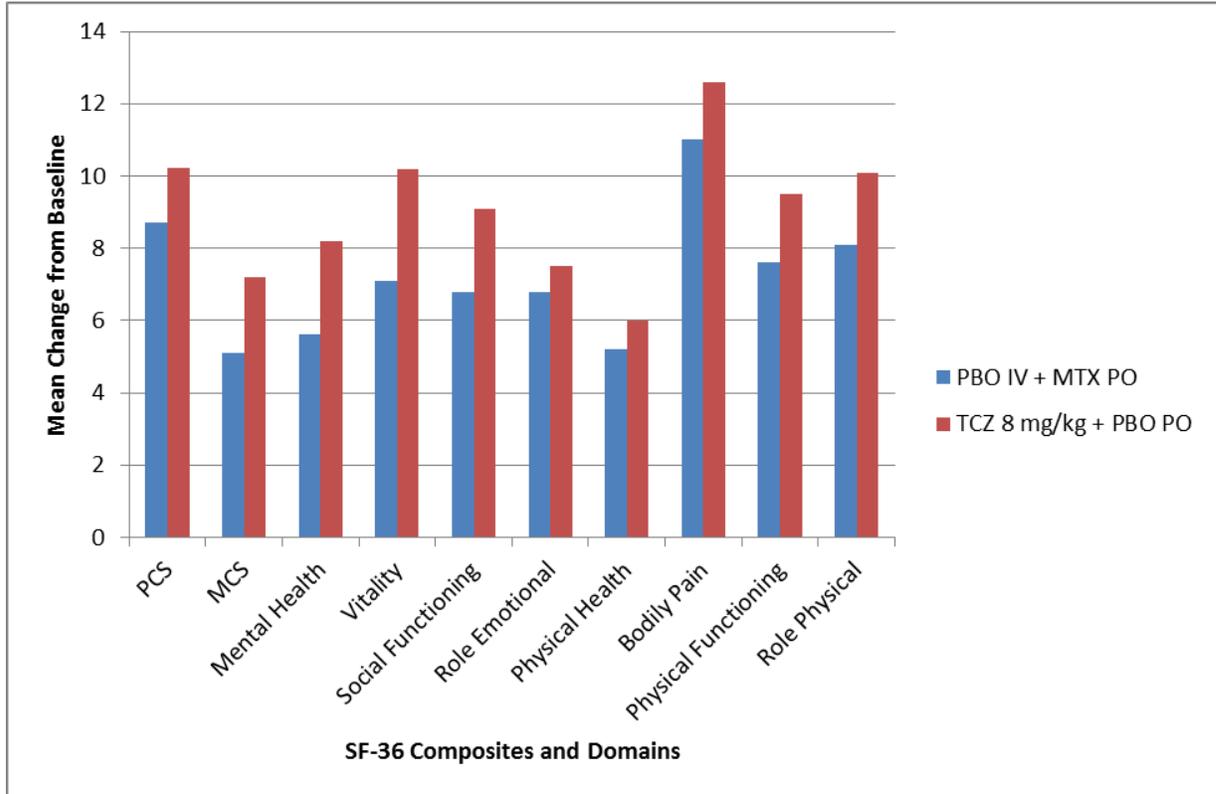
Study WA17823

Improvements in PCS and MCS were seen in all 3 treatment groups, however clinically relevant responses occurred earlier in the TCZ treatment groups. Clinically relevant improvement in mean PCS, was observed as early as Week 8 in both TCZ treatment arms, as compared with Week 24 in the placebo + MTX arm. Clinically relevant improvement in mean MCS, was reached at Week 24 in the TCZ 8 mg/kg + MTX arm, but not in the other treatment arms. Improvements were observed across the 8 domains, with greater mean improvements in the TCZ + MTX arms as compared to the placebo + MTX arm.

Study WA17824

Study 17824 compared treatment with TCZ 8 mg/kg + MTX to placebo + MTX; a lower dose of TCZ was not included in this study. Improvements exceeding the MCID were observed in the PCS and MCS scores in both treatment groups, with earlier improvements seen in the TCZ 8 mg/kg + MTX group. The clinically relevant improvements in PCS and MCS occurred as early as Week 8 in the TCZ 8 mg/kg + MTX group as compared to Week 16 for PCS and Week 24 for MCS in the placebo + MTX group. Confidence intervals were determined for the difference in adjusted means at Week 24; the lower limit of the 95% confidence interval for the treatment difference was >0 in the comparison of change in PCS scores, demonstrating superiority of TCZ 8 mg/kg + MTX as compared to placebo + MTX. Improvements in all 8 domains were observed in both treatment groups, with greater numerical improvement in the TCZ 8 mg/kg + MTX group (Figure 8).

Figure 7: Mean Change in SF-36 Composite and Domain Scores at Wk 24 (PP); WA17824



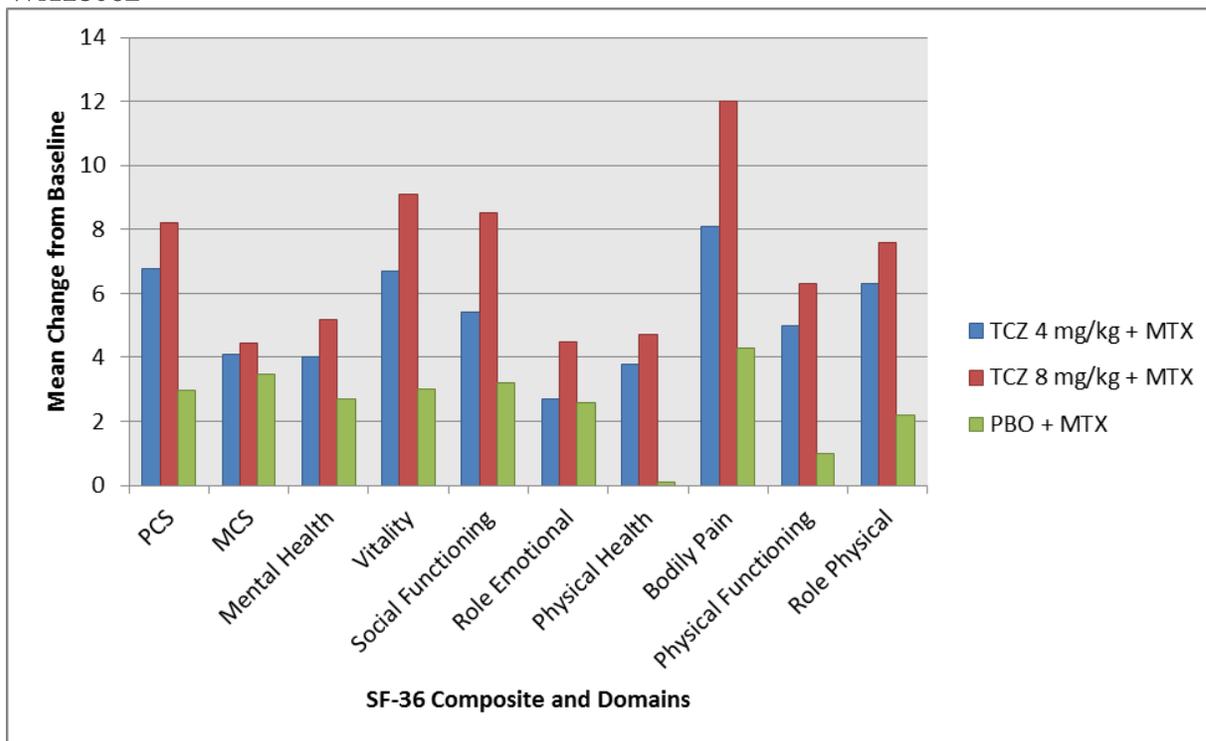
Adjusted mean change from baseline in PCS and MCS

Source: Adapted from Applicant submission, CSR WA17824; Tables 50, 51, 54.

Study WA18062

Similar results were observed in Study WA18062 with improvement demonstrated in PCS and MCS in all treatment groups, but earlier and increased improvement seen in the TCZ + MTX groups, as compared to the placebo + MTX group. At Week 24, the difference in the adjusted means for the PCS between TCZ 8 mg/kg + MTX group and the placebo + MTX group was statistically significant ($p=0.0020$). There was no significant difference in the adjusted mean improvements for the MCS between the treatment groups; however numerical improvement was seen in the TCZ + MTX groups as compared to the placebo + MTX group in unadjusted change in MCS. Improvements in the 8 domain scores were also greater in the TCZ + MTX groups at Week 24 (Figure 9).

Figure 8: Mean Change in SF-36 Composite and Domain Scores at Wk 24 (ITT); WA18062



Source: Adapted from Applicant submission, CSR WA18062

Study WA18063

In Study WA18063, greater and earlier increases were seen in the PCS and MCS scores in the TCZ 8 mg/kg + DMARD treatment group, as compared to the placebo + DMARD group. At Week 24, clinically relevant mean increases from baseline in PCS and MCS were observed for the TCZ 8 mg/kg + DMARD group, but not for the placebo + DMARD group (8.86 vs. 3.88 in TCZ and placebo for PCS, respectively, and 5.56 vs. 1.99 for MCS). The difference in adjusted means between the tocilizumab 8 mg/kg + DMARD group and the placebo + DMARD group at Week 24 was statistically significant for both the PCS and MCS scores. Clinically relevant improvement in the 8 domain scores was observed in the TCZ 8 mg/kg + DMARD group, while clinically relevant improvement was seen only in the bodily pain domain in the placebo + DMARD group.

SC Studies

In Study NA25220, there was greater improvement in both PCS and MCS in the group that received SC TCZ 162 mg q2w + DMARD, as compared to the group that received placebo + DMARD. This was supported by statistically significant improvement in the 8 domains in the tocilizumab treatment group as compared to the placebo group. In Study WA22762, mean change from baseline in SF-36 composite scores were generally comparable across treatments with TCZ IV 8 mg/kg + DMARD and TCZ 162 mg SC qw + DMARD (Table 4). The change in SF-36 composite scores exceeded the minimum clinically important difference for all tocilizumab treatment groups, but not for the placebo + DMARD group in Study NA25220.

Table 4: Mean Change in PCS and MCS scores by Treatment Group at Week 24 in SC Studies (ITT Population)

	Study WA22762		Study NA25220	
Mean Change at Wk24	TCZ 162 mg SC qw + DMARD	TCZ 8 mg/kg + DMARD	PBO SC q2w + DMARD	TCZ 162 mg SC q2w + DMARD
PCS	9.33	9.61	4.32	7.16*
MCS	6.23	6.75	3.01	6.12*

*p-value < 0.05

Source: Adapted from Applicant submission BLA 125472, Summary of Clinical Efficacy Table 35

The five IV tocilizumab studies described above showed clinically relevant and statistically significant improvements in SF-36 PCS score with treatment with tocilizumab as compared to placebo. Trends towards improvement in change from baseline in SF-36 MCS score were observed; these met statistical significance in studies WA17822 and WA18063. The improvements in MCS exceeded the minimum MCID for composite scores of 2.5-5 in all of the studies. Greater numerical improvement in the 8 domains was observed in the tocilizumab treatment groups as compared to the placebo treatment groups. The two SC studies demonstrate similar clinically relevant improvement in PCS and MCS with both SC and IV formulations of TCZ, both of which are superior to placebo. The FDA analyses, conducted by the statistical review team, were in general agreement with the analyses presented by the sponsor. Of note, these SF-36 results are consistent with the treatment effects observed in other RA products, as described in the published literature.^{xviii, xix, xx, xxi, xxii} Collectively, the SF-36 data from the Phase 3 clinical studies in this submission indicate that compared to placebo, tocilizumab 4 mg/kg IV, 8 mg/kg IV, and 162 mg SC, improves PCS, MCS, and all eight SF-36 domains in patients with active RA supporting the proposed indication.

8. Safety

No new safety information was submitted with this supplement. The safety information from tocilizumab development was reviewed in detail with the original BLA submissions and resulted in a boxed warning for serious infections including:

- Patients treated with Actemra[®] are at increased risk for developing serious infections that may lead to hospitalization or death. 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
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative

9. Advisory Committee Meeting

This supplemental application is for an ancillary claim for an already approved indication; thus no Advisory Committee meeting was warranted. An advisory committee meeting was held for the original BLA application 125276 on July 29, 2008.

10. Pediatrics

The pediatric issues were discussed in the reviews of the original BLA applications.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**—No issues
- **Other GCP issues**—No issues
- **DSI audits** – The OSI audits were conducted as part of the original BLA application (125276)
- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Proprietary name**

The trade name for tocilizumab, Actemra[®], has already been reviewed and approved.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments.**

None.

- **Physician labeling**

I recommend the following major revisions (all to Section 14, Clinical Studies):

1) Proposed SF-36 labeling language:

- The proposed language which includes the results of the summary scores as well as the 8 domains, is consistent with the decision following the Regulatory Briefing on September 20, 2013 to include all of the scores of the SF-36 to facilitate its

interpretation as a general health status measure. The term (b) (4) should be deleted and the phrase (b) (4) should be replaced by “general health status” for consistency with approved language used in describing SF-36 claims for more recently approved products (Xeljanz[®], Simponi Aria[®]).

At the time of this review, labeling discussions are ongoing. Proposed labeling revisions (new language in *red* and deletions are in ~~strikethrough~~):

14.1 Rheumatoid Arthritis-Intravenous Administration

“*General health status* (b) (4) was assessed by the Short Form Health Survey (SF-36) in Studies I-V. (b) (4) *Patients receiving Actemra demonstrated greater improvement from baseline compared to placebo in the Physical Component Summary (PCS), (b) (4) Mental Component Summary (MCS), and in all 8 domains of the SF-36.* - (b) (4)

14.2 Rheumatoid Arthritis-Subcutaneous Administration

“*General health status* (b) (4) was assessed by the Short Form Health Survey (SF-36) in Studies SC-I and SC-II. (b) (4) *patients receiving Actemra (b) (4) demonstrated greater improvement from baseline compared to placebo in the (b) (4) (PCS), (b) (4) (MCS), and in all 8 domains of the SF-36.* (b) (4)

2) Proposed PLLR labeling language

- The Applicant has submitted updates to the label to comply with the Pregnancy and Lactation Labeling Rule (PLLR). At the time of this review, labeling discussions are ongoing.
- **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. No changes are proposed to the Patient labeling/Medication guide with this submission.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplement with revisions to the labeling as discussed in Section Labeling above.

- **Risk Benefit Assessment**

The overall risk-benefit profile of tocilizumab in RA remains favorable, as determined at the time of the original BLA approvals and is not altered on the basis of this submission. The current submission supports the addition of SF-36 results in Section 14 of the prescribing information. Although the risks of tocilizumab are not minimal, these are balanced by a number of clinical benefits, which include reduction in patient's signs and symptoms and disease activity, improvement in physical functioning, and general health status.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

This supplement does not warrant new or modification of the previously released postmarketing risk evaluation and management strategies (REMS).

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

This supplement does not warrant new postmarketing requirements or commitments.

- **Recommended Comments to Applicant**

None.

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^v Oude Voshaar MA et al, Health Qual Life Outcomes. 2011 Nov 7;9:99

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^{vii} <http://www.sf-36.org/>

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/s/

RACHEL GLASER
08/03/2016

NIKOLAY P NIKOLOV
08/03/2016
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

STATISTICAL REVIEW(S)



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

Statistical Review

CLINICAL STUDY

sBLA / Sequence Number: 125472/ Seq 0077, 125276 / Seq 0189

Drug Name: Actemra[®] (tocilizumab)

Proposed Claim: SF-36 components and domains

Current Indication: Rheumatoid arthritis

Applicant: Genentech

Date(s): Received: 11-24-2015
PDUFA Due Date: 11-24-2016

Review Priority: Standard

Biometrics Division: Division of Biometrics II/Office of Biostatistics

Statistical Reviewer: Robert Abugov, Ph.D.

Concurring Reviewer: Gregory Levin, Ph.D.

Statistics Supervisor: Thomas Permutt, Ph.D. (Division Director)

Medical Division: Division of Pulmonary, Allergy, and Rheumatology Products

Clinical Team: Rachel Glaser, M.D. (Medical Reviewer)
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Project Manager: Colette Jackson

Keywords: NDA review, Clinical Studies

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1 EXECUTIVE SUMMARY

Genentech has proposed inclusion of additional endpoints, both components and all eight domains of Short Form 36 (SF-36), on the product label for Actemra (tocilizumab) administered as IV or SC for the treatment of patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDS).

Six placebo controlled, randomized, parallel group studies with DMARD add-on therapy confirm that Actemra improves SF36 compared to placebo. Statistically significant effects were seen in all six studies for the physical component and the physical function domain. Statistical significance of differences between Actemra and placebo was variable for the mental component and the other domains, however point estimates in these studies consistently indicated improvement by Actemra compared to placebo.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Actemra (tocilizumab), an interleukin-6 receptor antagonist, is already approved for the treatment of patients with moderately to severely active RA who have had an inadequate response to one or more DMARDS. In this supplement, the sponsor proposes for inclusion on the product label both components and all eight domains of SF-36.

2.1.2 History of Drug Development

Submissions evaluating tocilizumab IV (BLA 125276) and SC (BLA 125472) for the treatment of RA were reviewed by Drs Joan Buenconsejo and David Hoberman, with respective approvals for the IV and SC products granted January 8, 2010 and October 21, 2013 respectively. The reviews by Drs Buenconsejo and Hoberman provided an extensive account of the drug development history; highlights are summarized below.

2.1.2.1 Actemra IV

Phase 1 and 2 development of tocilizumab proceeded under IND 011972. In the pre-phase 3 meeting held on September 9, 2004 regarding intravenous (IV) administration, the Division discussed alternative endpoints, with an emphasis on percentage of patients with a clinically

meaningful response. In a telecom meeting on September 8, 2005, the sponsor was advised to carefully define which significance results in the analysis hierarchy would provide grounds for product approval. On November 1, 2006, the Division noted that statistical analyses should be prespecified for all endpoints to be evaluated for inclusion on the product label.

The sponsor submitted results and associated datasets for the IV product in BLA 125276 on November 19, 2007. Four randomized, double-blind, parallel arm, placebo-controlled studies with methotrexate as add-on therapy (WA17822, WA17823, WA18062, and WA18063), demonstrated that both 4 mg/kg q4w and 8 mg/kg q4w were superior to placebo for the primary endpoint, ACR20 at week 24, as well as for ACR50, ACR70, and all components of ACR response, such as swollen and tender joint counts, health assessment questionnaire disability index (HAQ-DI), patient global assessment, and patient pain visual assessment scale. Approval for Actemra IV was granted for both the 4 mg/kg q4w and 8 mg/kg q4w doses on January 8, 2010.

2.1.2.2 Actemra SC

Like Actemra IV, early development of tocilizumab for subcutaneous (SC) administration was conducted under IND 011972. On March 29, 2009, the Division provided for the sponsor a special protocol assessment (SPA) for proposed 24 week study WA22762 to evaluate non-inferiority of tocilizumab SC to tocilizumab IV. The Division noted that missing data would be a review issue, and that several approaches to the problem, including analyses of both the intent-to treat (ITT) and per-protocol (PP) populations would be required. The Division also agreed with the proposed primary endpoint, ACR20, to be evaluated using a non-inferiority margin of 10%. On June 11, 2010, the Division provided for the sponsor an SPA for study NA25220, designed to evaluate superiority of tocilizumab SC + methotrexate (MTX) to placebo plus MTX using primary endpoint ACR20. The Division agreed with the use of ACR20 as the primary endpoint, but noted that superiority for that endpoint would not serve as a bridge to claim superiority to all endpoints claimed for Actemra IV but not tested in Actemra SC. The Division reiterated this position in minutes to a type A meeting communicated to the sponsor on September 28, 2010.

The sponsor submitted results and associated datasets for tocilizumab SC in BLA 125472 on December 21, 2012. Non-inferiority of SC to IV dosing was established in study WA22762, with the lower 95% confidence interval for the difference in week 24 ACR20 response rates exceeding the non-inferiority margin of -10%. Further, superiority of tocilizumab SC + MTX to placebo + MTX was established in study NA25220. Actemra SC (tocilizumab 162 mg SC q2w) was approved for RA on October 21, 2013.

2.2 Data Sources

For Actemra IV, this sBLA submission references BLA 125472 sequence 0002, currently located at X:\BLA125276\0002\m5\datasets\wa17823-year-1\analysis

For Actemra SC, this sBLA submission references BLA 125472 sequence 000, currently located at \\Cdsesub1\evsprod\BLA125472\0000\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of data and analyses provided in this submission was adequate.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

This submission proposes to add, to Section 14 of the current Actemra product label, claims for improvement in all domains of SF-36. The sponsor's proposal is based on eight phase 3, randomized, parallel-arm, double-blind, placebo- or active-controlled trials in patients with moderately to severely active RA. Five of the trials (Table 1 and Table 2) address efficacy of Actemra administered intravenously (IV), and three of the trials (Table 3) address efficacy of Actemra administered subcutaneously (SC).

In trials WA17822 (study 22), WA17823 (study 23), and WA18062 (study 62), patients were randomized to placebo (Pbo), tocilizumab IV 4 mg/kg q4w (TIV4), or to tocilizumab IV 8 mg/kg q4w (TIV8). In trials WA17824 (study 24) and WA18063 (study 63), patients were randomized to Pbo or TIV8. In study 24, all patients on placebo were switched to TIV8 at study week 8, with placebo patients limited to sites in the USA, Canada, or Israel. To examine efficacy of subcutaneous administration, trial NA25220 (study 20) randomized patients to Pbo or tocilizumab 162 mg administered subcutaneously q2w (TSC). Treatments were given as add-ons to therapy with MTX (studies 22, 23, 24, and 62) or other non-biologic DMARDs (studies 63 and 20).

Studies 22 and 23 enrolled patients with inadequate response to MTX, study 24 enrolled patients who were naive to MTX or who had discontinued treatment with MTX for reasons other than lack of efficacy or intolerance, studies 62 and 63 enrolled patients with an inadequate response to TNF inhibitors, and study 20 enrolled patients with inadequate response to DMARDS, including TNF inhibitors. Study 24 enrolled patients who had RA for at least 3 months, while studies 20, 22, 23, 62, and 64 enrolled patients who had RA for at least 6 months.

Study 24 was originally designed to demonstrate noninferiority of TIV8 to MTX. A pure placebo arm without MTX add-on was provided at certain sites, as an internal control to evaluate assay sensitivity. Results comparing TIV8 to pure placebo will not be addressed here.

Of the three trials for subcutaneous Actemra administration (Table 3), only study 20 included a placebo control; the other two trials, WA22762 (study SC62).and MRA229JP, were bridging studies to compare IV and SC administration. Study MRA229JP was conducted only in Japan and will not be considered further in this review.

Double blinded rescue was provided at the investigator's and patient's discretion for patients with < 20% improvement in tender joint count and swollen joint count. In study 23, rescue consisted of TIV8 for patients randomized to TIV4 or TIV8, and TIV4 or TIV8 for patients randomized to Pbo. In studies 22 and 62, rescued patients received TIV8, in study 63 background DMARD dose was adjusted for rescue patients but no provisions were made for increasing their dose of tocilizumab. In study 24, only patients at sites participating in the placebo substudy, i.e. all sites in the USA, Canada, or Israel, were eligible for rescue; such patients were administered TIV8 with discontinuation of MTX. In study 20, patients on Pbo were rescued with TSC.

Among rescued patients, data collection for SF-36 was continued to study endpoint but data after rescue was not included in the analyses.

Table 1. Randomized Phase 3 Efficacy Studies for Actemra IV, BLA 125276

Study¹	Design	Population
WA17822 (III)	Pbo TIV4 TIV8 Add-on to MTX DB, PA R W16 to TIV8 Pbo to W24	RA ≥ 6 months ≥ 18 years Inadequate resp to MTX Stable or no OCS All non-study DMARDs washed out SJC ≥ 6 and TJC ≥ 8 CRP ≥ 1 mg/dL or ESR ≥ 28 mm/hr Functional ACR class IV excluded N=623 1:1:1 strat: site
WA17823 (II)	Pbo TIV4 TIV8 Add-on to MTX DB, PA R W16 to TIV in DB incremental increases	RA ≥ 6 months ≥ 18 years Inadequate resp to MTX SJC ≥ 6 and TJC ≥ 8 CRP ≥ 1 mg/dL or ESR ≥ 28 mm/hr All non-study DMARD washed out SJC ≥ 6 and TJC ≥ 8 CRP ≥ 1 mg/dL or ESR ≥ 28 mm/hr N=1196 1:1:1 strat: site

Source: Reviewer

¹Roman numerals correspond to study number on current pi.

Pbo Placebo, TIV4 tocilizumab IV mg/kg q4w, TIV8 tocilizumab IV 8 mg/kg q4w, MTX oral or parenteral methotrexate 10 to 25 mg q1w. DB double blind, PA parallel arm, R rescue if < 20% improvement TJC and SJC if patient requests and deemed necessary by investigator, S22 MTX oral or parenteral methotrexate 10 to 25 mg WW, OCS oral corticosteroids, DMARD disease modifying anti-rheumatic drug, SJC swollen joint count, TJC tender joint count, CRP C-reactive protein, ESR erythrocyte sedimentation rate, ACR American College of Rheumatology

Table 2. Randomized Phase 3 Efficacy Studies for Actemra IV, BLA 125276

Study	Design	Population
WA17824 (I)	MTX TIV8 Pbo ¹ DB, PA, DD R W1 to W7 DB to W24 Pbo to W8	RA ≥ 3 months ≥ 18 years MTX naive or discontinued not due to lack of efficacy or intolerance Stable or no OCS All non-study DMARDs washed out SJC ≥ 6 and TJC ≥ 8 CRP ≥ 1 mg/dL or ESR ≥ 28 mm/hr Functional ACR class IV excluded N=673 1:1 strat: site, RA dur (≤2, >2 years)
WA18062 (V)	Pbo TIV4 TIV8 Add-on to MTX PA, DB R W16 to TIV8 Pbo to W24	RA ≥ 6 months ≥ 18 years Inadequate resp to anti-TNF Stable or no OCS Anti-TNF washed out SJC ≥ 6 and TJC ≥ 8 CRP ≥ 1 mg/dL or ESR ≥ 28 mm/hr Functional ACR class IV excluded N=499 1:1:1 strat: site
WA18063 (IV)	Pbo TIV8 Add-on to DMARD PA, DB R W16 DMARD adj Pbo to W24	RA ≥ 6 months ≥ 18 years Inadequate resp to anti-TNF Anti-TNF washed out Stable or no OCS No concomitant biologics SJC ≥ 6 and TJC ≥ 8 Functional ACR class IV excluded N=1220 2:1 strat: site

Source: Reviewer

¹ Pbo in study 24 consisted of placebo up to week 8 followed by TIV8 to W24. For other abbreviations refer to footnote of Table 1

DD double dummy, TNF tumor necrosis factor

Table 3. Randomized Phase 3 Efficacy Studies for Actemra SC, BLA 125472

Study	Design	Population
WA22762 (SCI)	TSC TIV8 add-on to DMARD DB, DD, PA AC DB to W24	RA \geq 6 months \geq 18 years Inadequate resp to DMARD incl anti TNF Stable or no OCS Anti-TNF and bDMARD washed out CRP \geq 1 mg/dL or ESR \geq 28 mm/hr N=1262 1:1 strat: region, weight
NA25220 (SCII)	TSC Pbo add-on to DMARD DB, PA R W12 Pbo to W24	RA \geq 6 months \geq 18 years Inadequate resp to DMARD incl anti-TNF Stable or no OCS Anti-TNF and bDMARD washed out N=656 2:1 strat: region weight
MRA229JP (Japan Only)	TSC TIV8 DB, DD, PA, AC DB to W24	RA \geq 6 months \geq 18 years Inadequate resp to DMARD or incl anti-TNF Stable or no OCS No anti-TNF or DMARD Tocilizumab naive N=347 1:1

For abbreviations refer to footnote of Table 1

3.2.2 Statistical Methodologies

For this submission, the sponsor provided results from descriptive analyses of pooled data from the IV studies and then from both of the non-Japan SC studies. However, pooled results from multiple studies are not generally acceptable for determining whether claims should be included on the product label. The sponsor also provided references to analyses in the original study reports, with ANOVA or ANCOVA (studies 20, 22, 23 62, 63), or purely descriptive analyses (studies 24, 62) for change from baseline of the mental and physical components and purely descriptive analyses of domain results (means and standard deviations) for studies 22, 23, 24, 62, and 63.

For this review, change from baseline SF-36 components and domains at week 24 were analyzed in a consistent manner, using ANCOVA conducted according to analysis plans prespecified for key secondary continuous endpoints. For Actemra IV, the ANCOVA used the randomization stratification factors as independent variables, while for Actemra SC study 20, the ANCOVA used the randomization stratification factors plus baseline value as independent factors. In Actemra SC study sc62, all key secondary endpoints were binary, with planned analyses for continuous variables summarizing means and standard deviations; therefore for this review, similar to Actemra SC study 20, an ANCOVA was conducted on study sc62 data with randomization stratification factors plus baseline value as independent factors. To facilitate interpretation, results from all ANCOVA (Appendix 6) were converted into forest plots (Figure 1 through Figure 20).

Analyses of SF-36 for non-inferiority study 24 included patients in the per-protocol population, defined as those patients who met inclusion criteria on the case report forms and remained on randomized treatment without rescue medication or protocol violations. Analyses of other studies included the intent to treat population but SF-36 scores were set to missing after administration of rescue medication. No imputations of missing data were conducted.

Statistical tests were conducted at the two-sided 0.05 level of significance, and confidence intervals were calculated as two sided at the 95% level of confidence.

Type 1 error in the face of multiple endpoints was controlled through extensive use of sequential analysis hierarchies. Failures before SF36 in the analysis hierarchies occurred in studies 23 and 24.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient demographics in the original submission for all five phase 3 studies were reviewed by Drs. Buenconsejo and Hoberman, who found no noticeable imbalances in demographic and baseline characteristics between treatment groups.

Consistent with efficacy, a brief disposition summary across the placebo-controlled trials 20, 22, 23, 24, 62, and 63 (Table 4) showed consistently higher rates of rescue among patients randomized to placebo compared to patients randomized to tocilizumab. And, consistent with a dose response effect, a higher percentage of patients randomized to TIV4 were rescued compared to patients randomized to TIV8.

3.2.4 Results and Conclusions: SF-36 Week 24

Product label revisions proposed by the sponsor contain claims for both components and all eight domains of SF-36. As mentioned earlier in this review, due to earlier failures in the sequential analysis hierarchies, SF-36 is only an exploratory variable in studies 23 and 24, and bounds of actual confidence limits are wider than those presented below.

3.2.4.1 Forest Plot Analyses

For the physical component summary and the physical function domain, all studies showed differences between TIV4 and Pbo and between TIV8 and Pbo (Figure 1, Figure 3, Figure 11, and Figure 13). For all other domains, as well as for mental component summary, trends consistently favored treatment (Figure 2, Figure 4 through Figure 10, Figure 12, and Figure 14 through Figure 20). Only one point estimate favored placebo rather than treatment, the comparison between TIV4 and Pbo in the social function domain for study 23; even then the point estimate comparing TIV8 and Pbo for that domain favored treatment. Subcutaneous dosing from study 20 was included on all of the above figures, showing no consistent difference between SC and IV routes of administration.

In summary, there is support for the sponsor's proposed inclusion on the label that:

[REDACTED] (b) (4)

However, although the trends do favor improvement, there is no formal assessment whether such improvements were [REDACTED] (b) (4) and I recommend deletion of that term from final labeling.

Figure 1. Change from Baseline SF-36 Physical Component Summary, Week 24, TIV4 vs Pbo

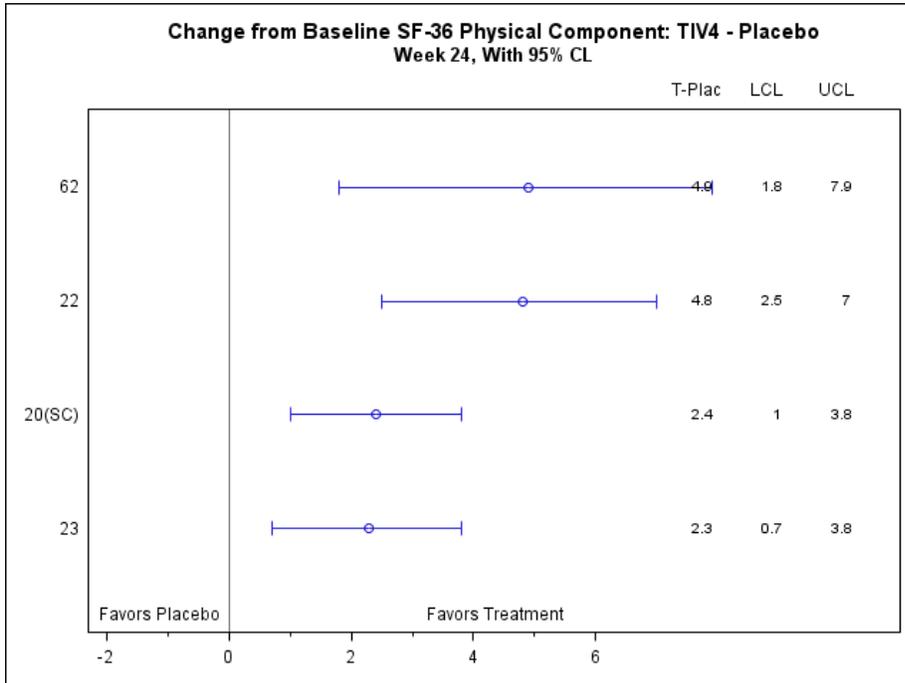


Figure 2. Change from Baseline SF-36 Mental Component Summary, Week 24, TIV4 vs Pbo

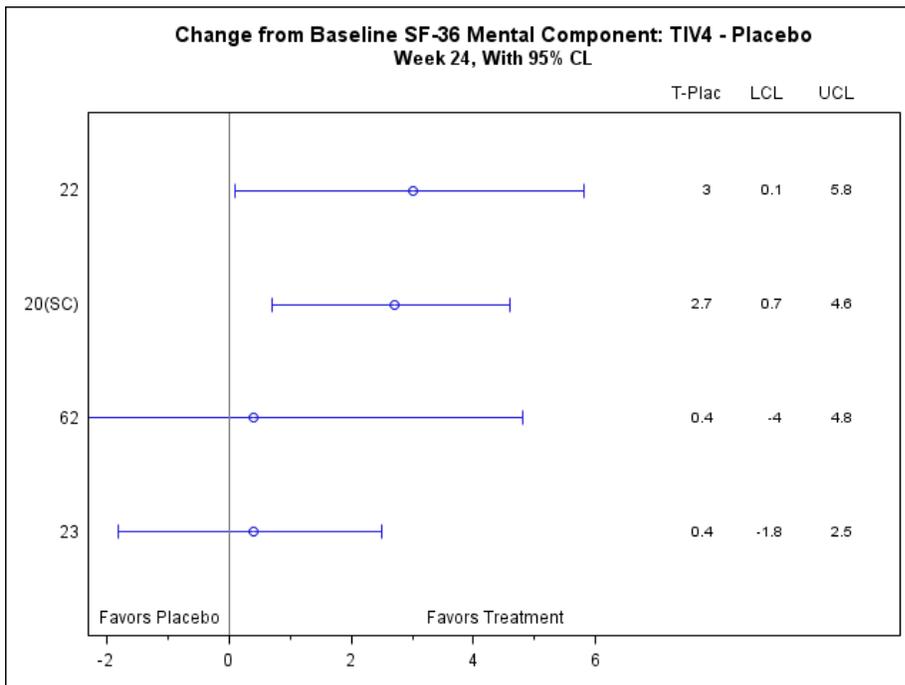


Figure 3. Change from Baseline SF-36 Physical Function Domain, Week 24, TIV4 vs Pbo

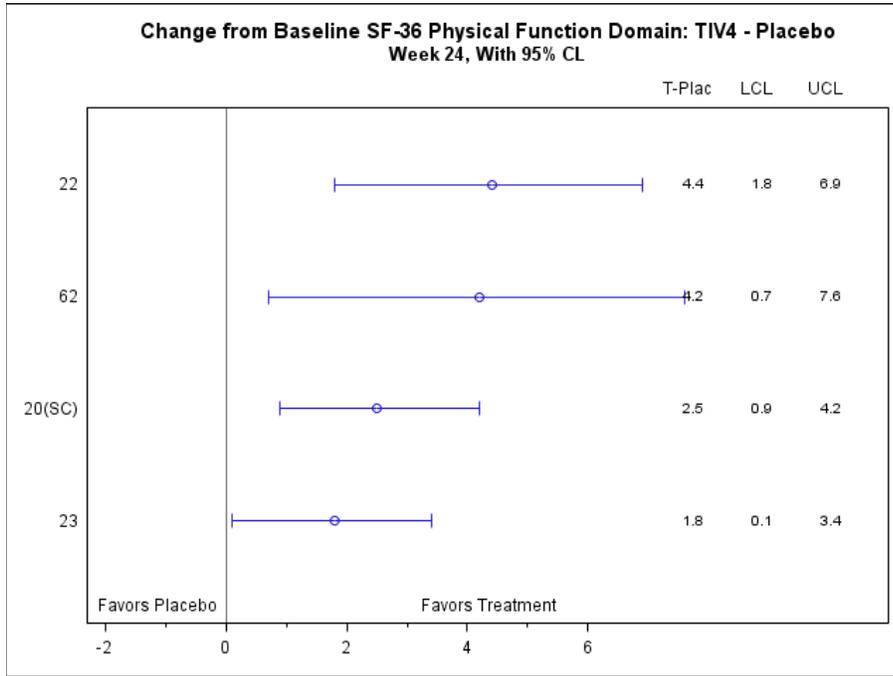


Figure 4. Change from Baseline SF-36 Role Physical Domain, Week 24, TIV4 vs Pbo

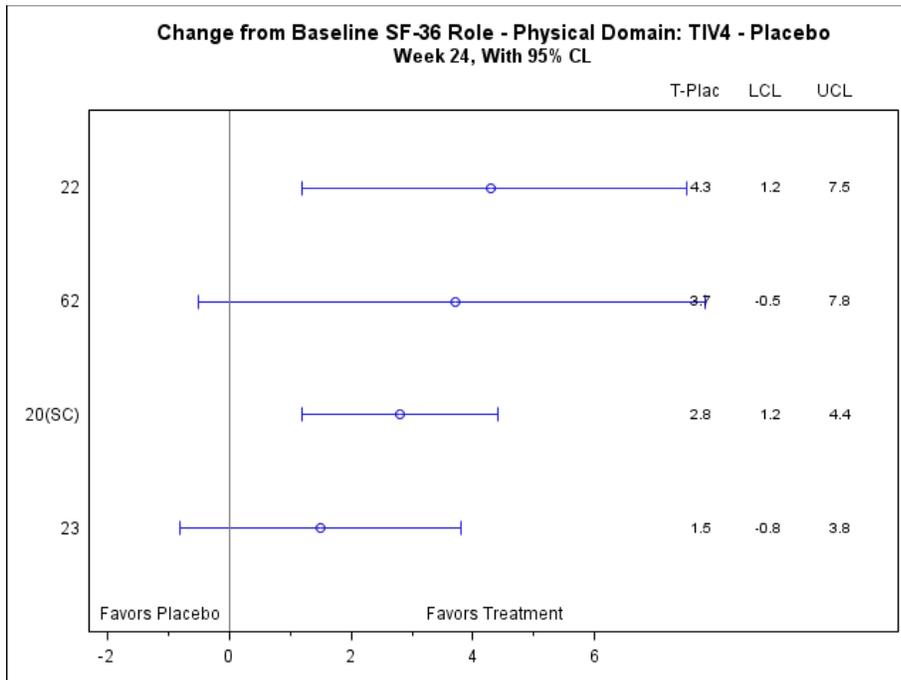


Figure 5. Change from Baseline SF-36 Bodily Pain Domain, Week 24, TIV4 vs Pbo

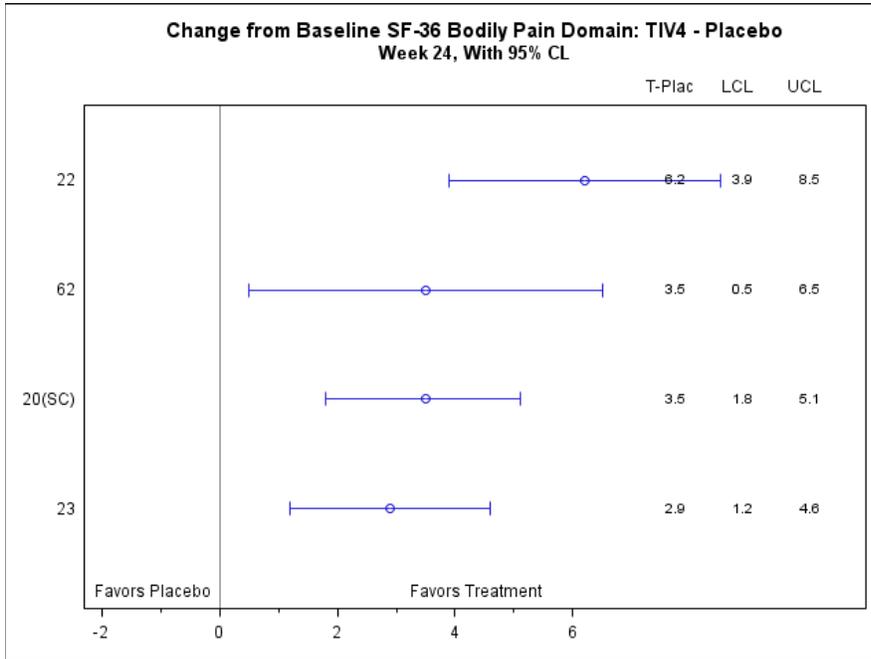


Figure 6. Change from Baseline SF-36 General Health Domain, Week 24, TIV4 vs Pbo

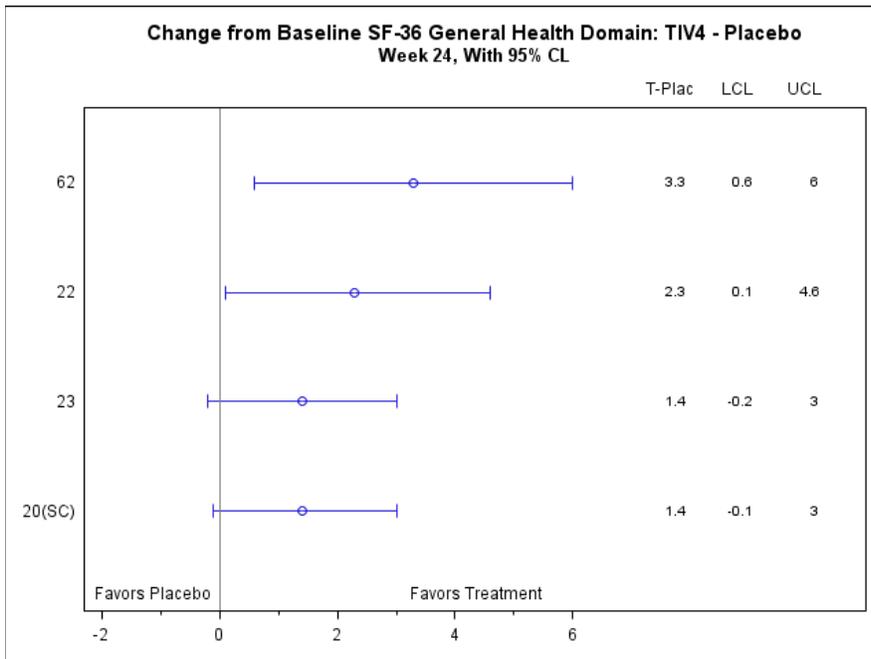


Figure 7. Change from Baseline SF-36 Vitality Domain, Week 24, TIV4 vs Pbo

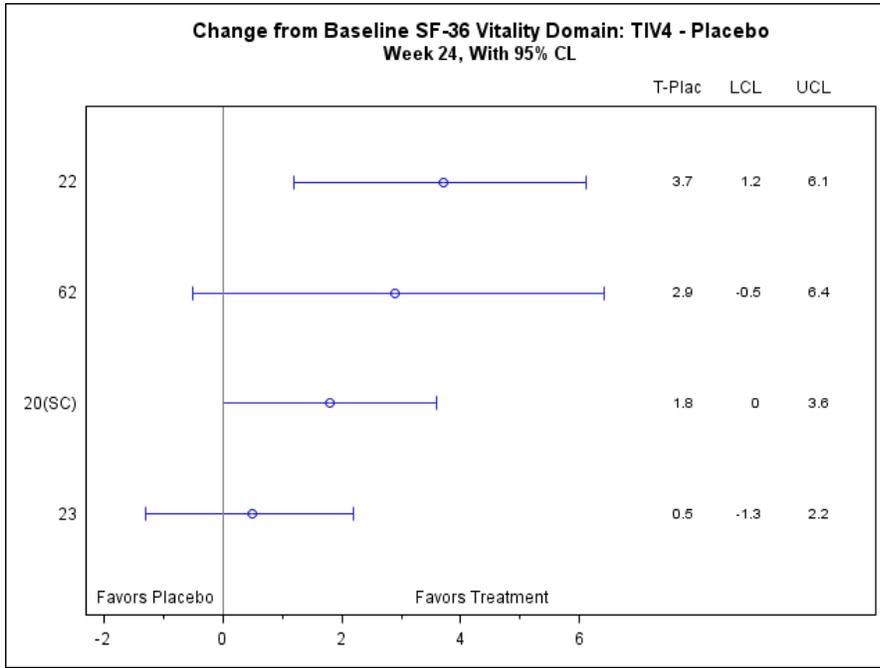


Figure 8. Change from Baseline SF-36 Social Function Domain, Week 24, TIV4 vs Pbo

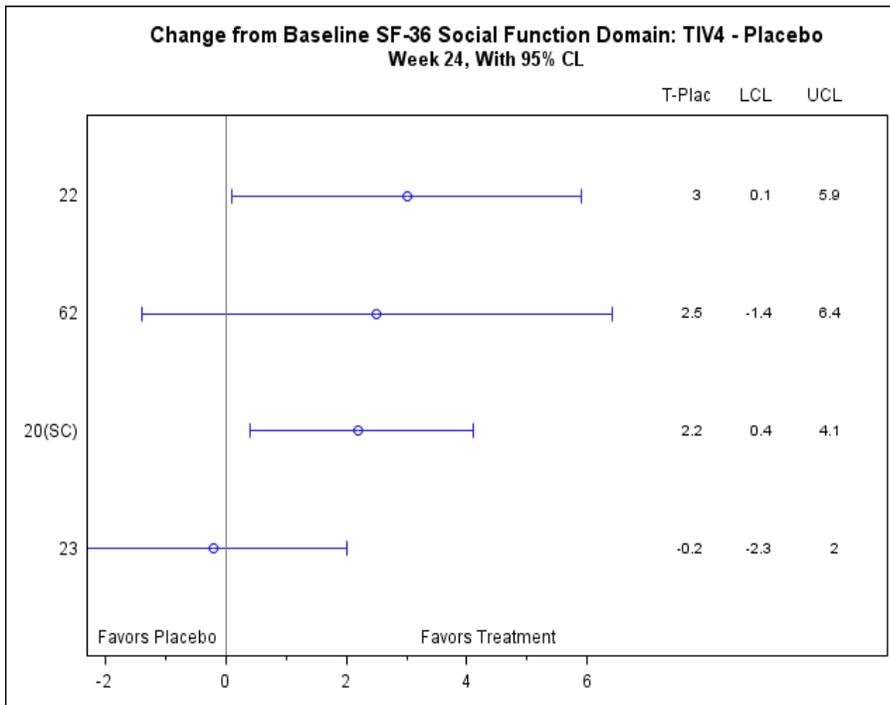


Figure 9. Change from Baseline SF-36 Role-Emotional Domain, Week 24, TIV4 vs Pbo

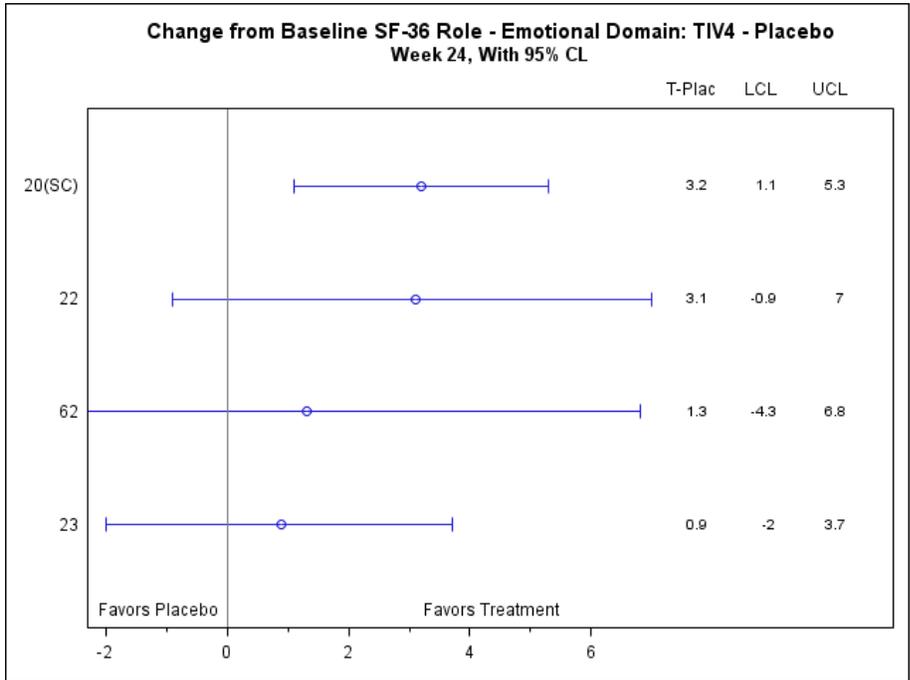


Figure 10. Change from Baseline SF-36 Mental Health Domain, Week 24, TIV4 vs Pbo

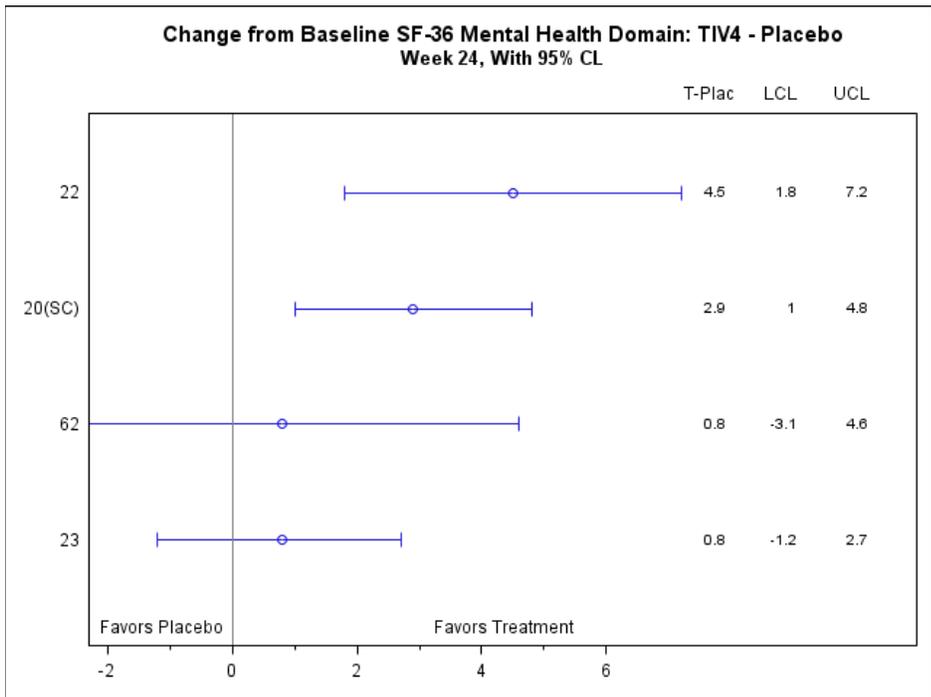


Figure 11. Change from Baseline SF-36 Physical Component Summary, Week 24, TIV8 vs Pbo

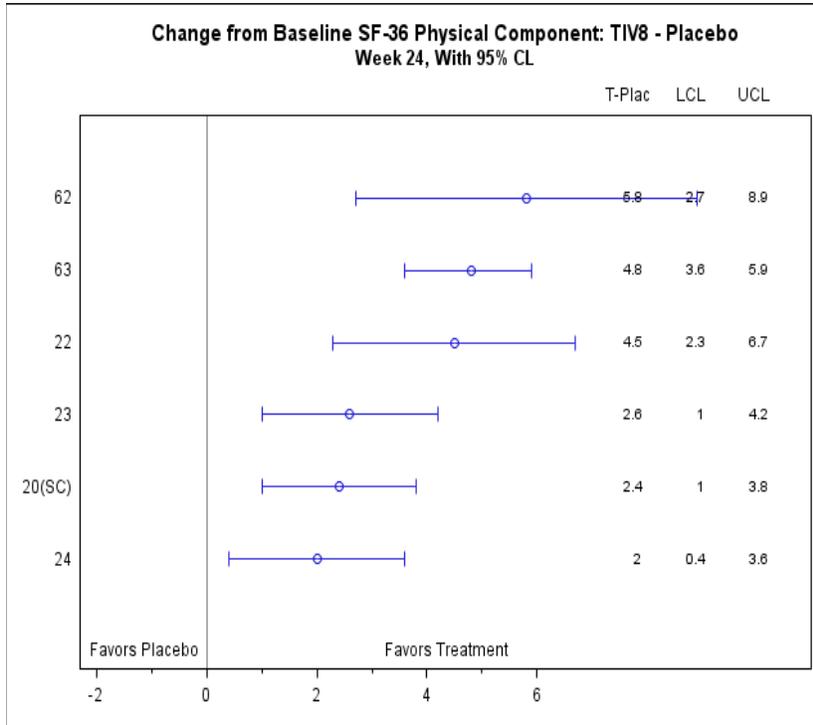


Figure 12. Change from Baseline SF-36 Mental Component Summary, Week 24, TIV8 vs Pbo

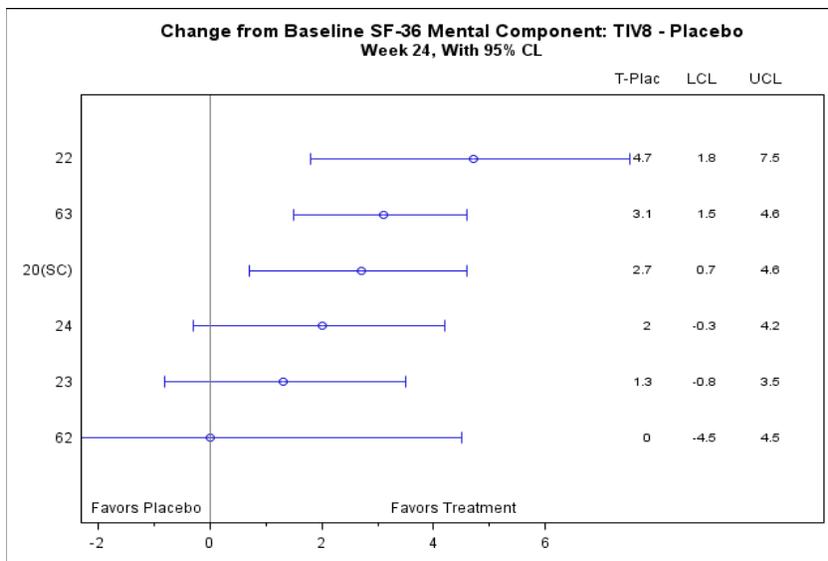


Figure 13. Change from Baseline SF-36 Physical Function Domain, Week 24, TIV8 vs Pbo

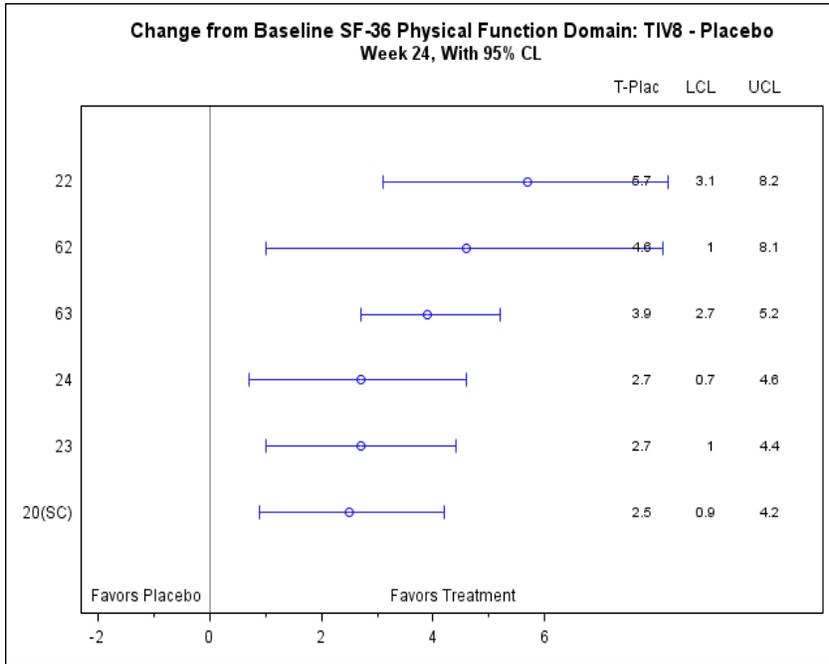


Figure 14. Change from Baseline SF-36 Role Physical Domain, Week 24, TIV8 vs Pbo

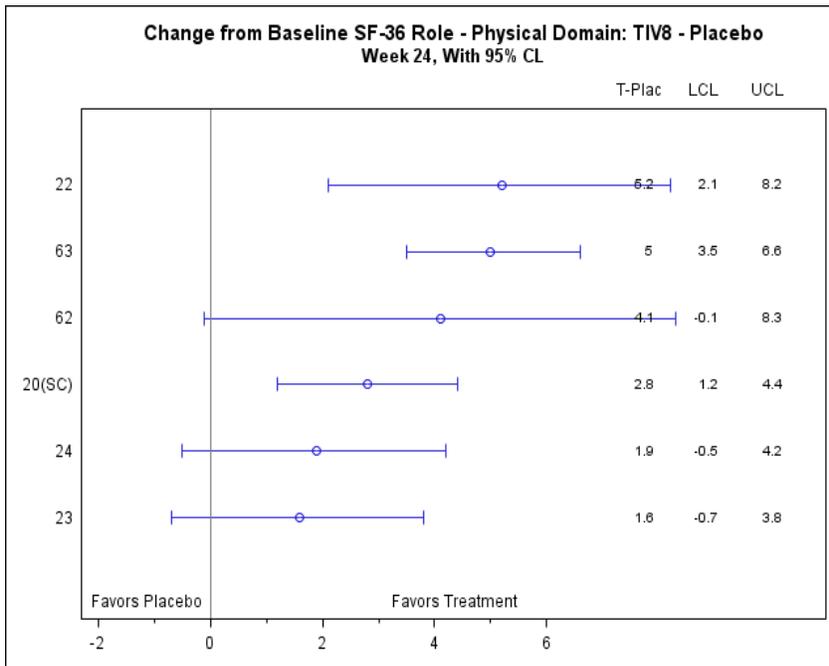


Figure 15. Change from Baseline SF-36 Bodily Pain Domain, Week 24, TIV8 vs Pbo

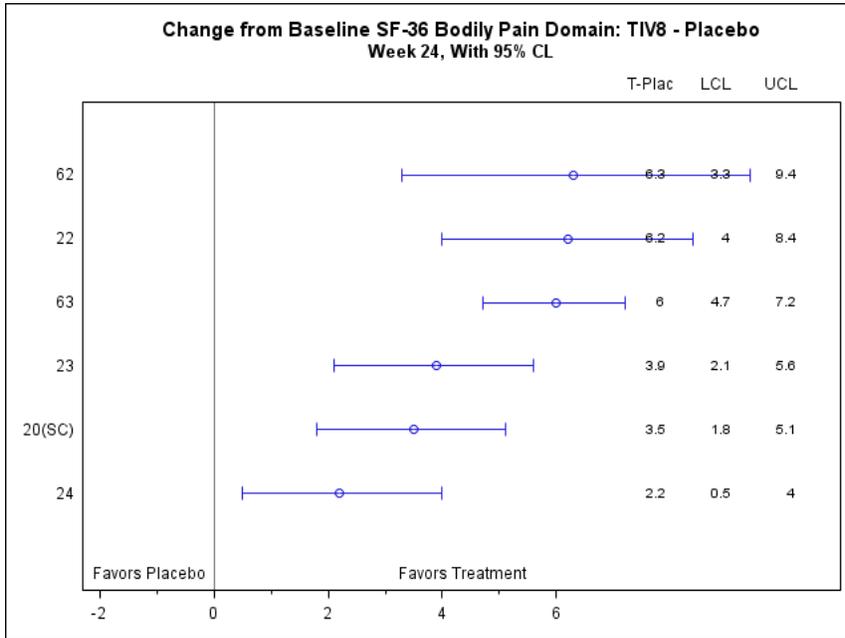


Figure 16. Change from Baseline SF-36 General Health Domain, Week 24, TIV8 vs Pbo

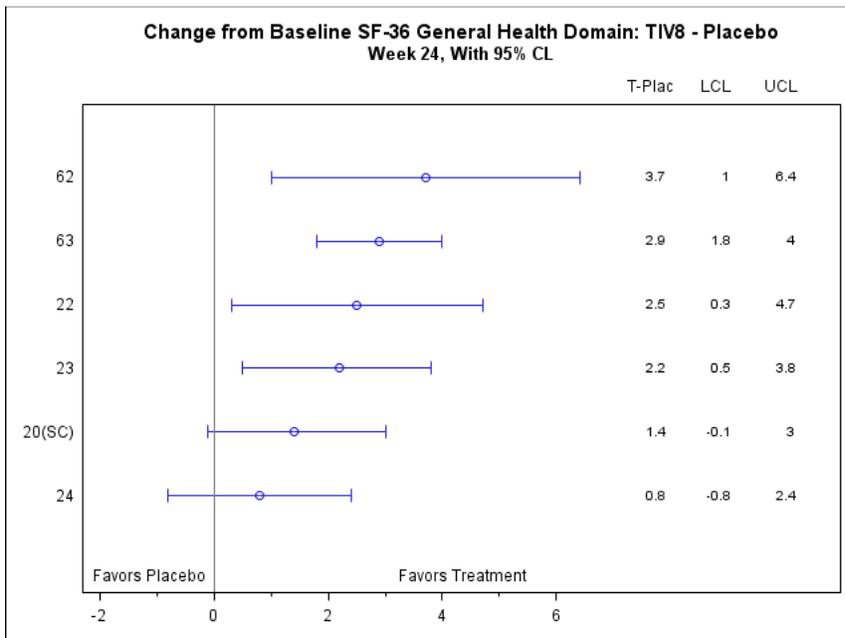


Figure 17. Change from Baseline SF-36 Vitality Domain, Week 24, TIV8 vs Pbo

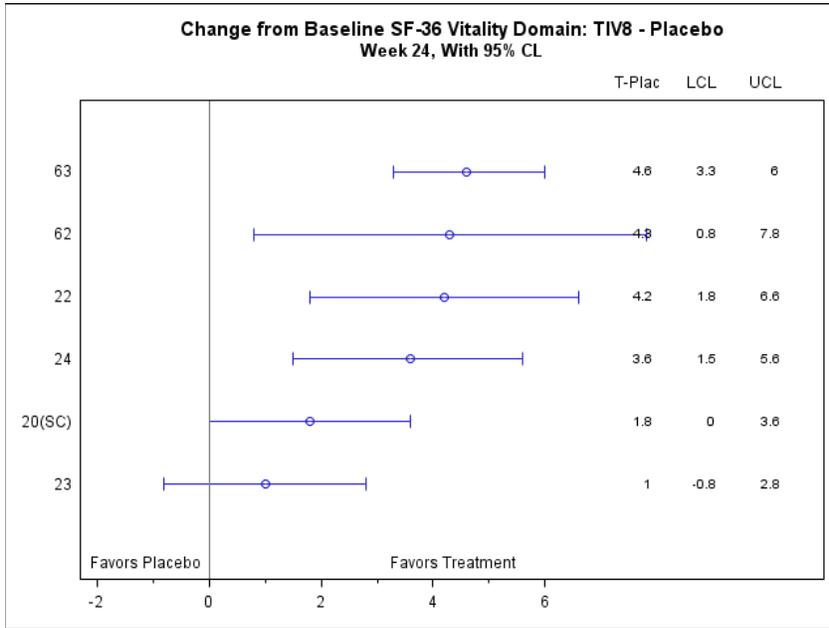


Figure 18. Change from Baseline SF-36 Social Function Domain, Week 24, TIV8 vs Pbo

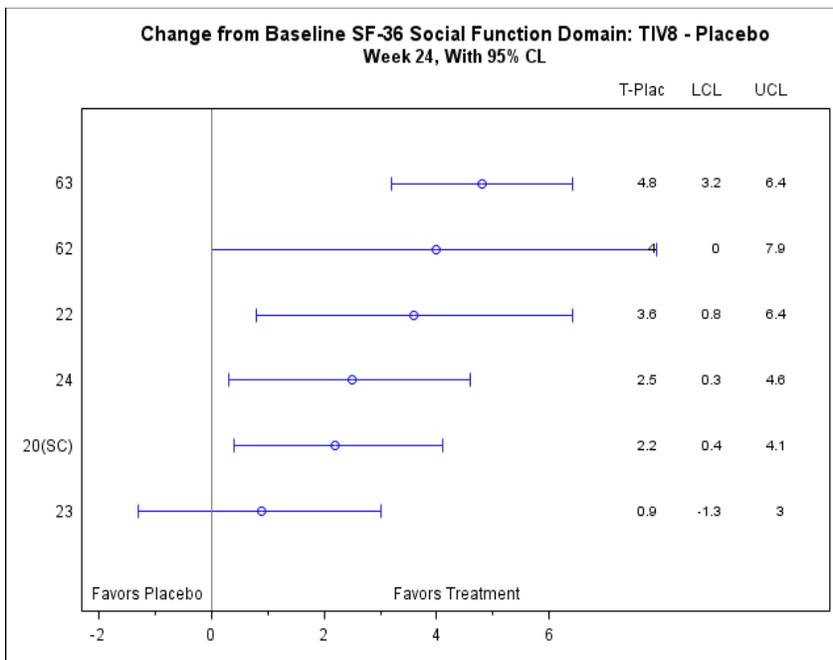


Figure 19. Change from Baseline SF-36 Role-Emotional Domain, Week 24, TIV8 vs Pbo

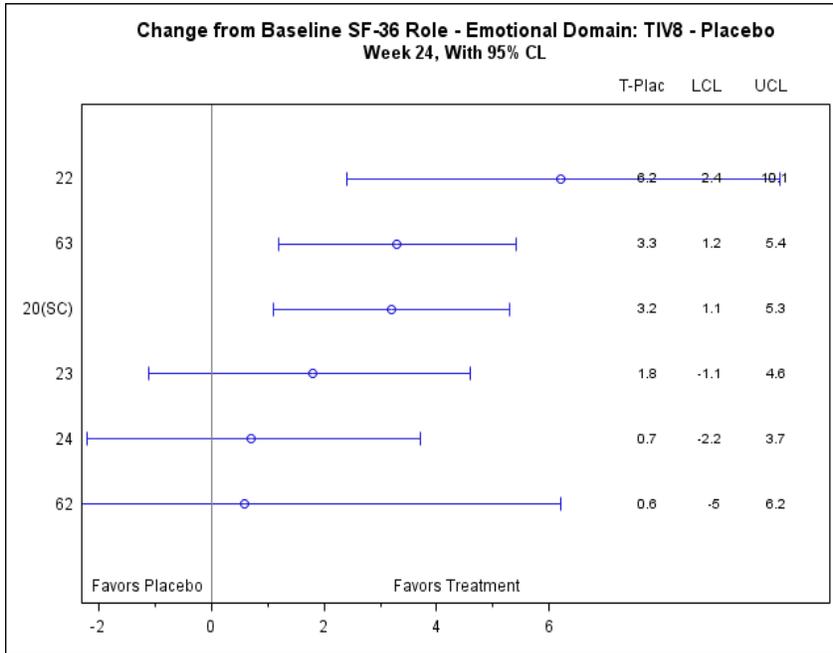
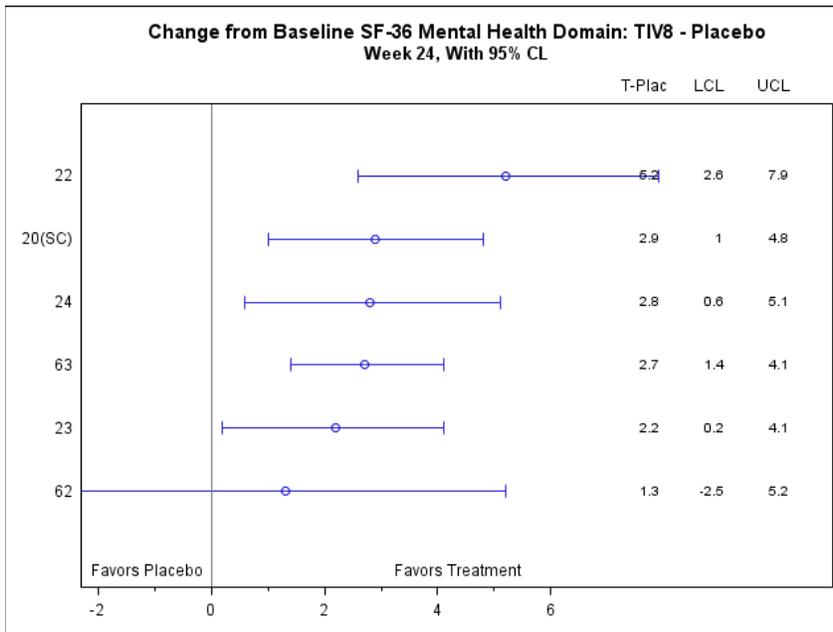


Figure 20. Change from Baseline SF-36 Mental Health Domain, Week 24, TIV8 vs Pbo



source: ancova.sas, forest plots.sas, data for study 24 limited to sites participating in the placebo controlled substudy

3.2.4.2 Bridging Study SC62

Differences between TIV8 and TSC in all components and domains of SF-36 in bridging study SC62 (Table 11) were small and tended to be less than differences between TIV8 and placebo and in the same range as differences between TIV4 and TIV8 (Table 6, Table 7, and Table 8), suggesting that both TIV8 and TSC have comparable effects.

3.3 Evaluation of Safety

Product safety has already been addressed in reviews for original approval of Actemra IV and Actemra SC.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Findings in special subgroups and populations for the primary endpoint have already been addressed in reviews for original approval of Actemra IV and Actemra SC. Impacts on the secondary endpoints evaluated in this review will not be further addressed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

No important statistical issues were identified in this submission.

5.2 Collective evidence

The collective evidence demonstrates that Actemra IV and SC improve all components and domains of SF-36. Six out of six placebo-controlled studies showed TIV8 and TSC significantly superior to placebo for change from baseline SF-36 physical component summary and the physical function and bodily pain domains. For the SF-36 mental component summary and all other domains, at least three of the six studies showed statistically significant differences between TIV8 and placebo. Similar results were seen for TIV4. All point estimates were consistent with superiority of Actemra over placebo for all components and domains, with the exceptions of mental component summary for TIV8 in study 62 and social function domain for TIV4 in study 23.

5.3 Conclusions and Recommendations

Genentech has proposed inclusion of additional endpoints, both components and all eight domains of Short Form 36 (SF-36), on the product label for Actemra (tocilizumab) administered as IV or SC for the treatment of patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDS).

Six placebo controlled, randomized, parallel arm studies with DMARD add on therapy confirm that Actemra improves SF36 compared to placebo. Statistically significant effects were seen in all six studies for the physical component and the physical function domain. Statistical significance of differences between Actemra and placebo was variable for the mental component and the other domains, however point estimates in these studies consistently indicated improvement by Actemra compared to placebo.

5.4 Labeling Recommendations

The sponsor proposes the following labeling language:

[REDACTED] (b) (4)

Implemented labeling language should be consistent with the following revised wording:

"Patients receiving Actemra [REDACTED] (b) (4) demonstrated greater improvement from baseline in the Physical Component Summary, Physical Component Summary, and in all 8 domains of the SF-36."

6 Appendix: Supplemental Tables

Table 5. Change from Baseline SF-36 Components and Domains, Study 20

Score	Treatment (N)		Difference (p-value) (95% CI) TSC-Pbo
	TSC (348)	Pbo (124)	
Physical Health CS	5.33	2.91	2.42 ($<.001$) (1.04, 3.79)
Mental Health CS	6.51	3.84	2.66 (.007) (0.74, 4.59)
Physical Function	4.42	1.87	2.54 (.003) (0.85, 4.24)
Role Physical	6.17	3.37	2.8 ($<.001$) (1.18, 4.42)
Bodily Pain	8.31	4.83	3.48 ($<.001$) (1.83, 5.13)
General Health	5	3.56	1.44 (.071) (-0.12, 3)
Vitality	6.32	4.54	1.79 (.048) (0.02, 3.56)
Social Function	5.63	3.38	2.25 (.018) (0.38, 4.11)
Role Emotional	6.85	3.64	3.21 (.003) (1.09, 5.32)
Mental Health	6.66	3.78	2.88 (.003) (0.95, 4.81)

Table 6. Change from Baseline SF-36 Components and Domains, Study 22

Param	Treatment (N)			Difference (p-value) (95% CI)		
	TIV8 (192)	TIV4 (187)	Pbo (190)	TIV8-Pbo	TIV4-Pbo	TIV8-TIV4
Physical Health CS	9.47	9.73	4.97	4.5 (<.001) (2.32, 6.68)	4.76 (<.001) (2.54, 6.97)	-0.26 (0.804) (-2.3, 1.78)
Mental Health CS	7.31	5.65	2.65	4.65 (0.001) (1.85, 7.46)	3 (0.039) (0.15, 5.85)	1.66 (0.215) (-0.97, 4.28)
Physical Functioning	8.18	6.9	2.52	5.66 (<.001) (3.14, 8.17)	4.38 (<.001) (1.81, 6.95)	1.28 (0.286) (-1.07, 3.63)
Role Physical	9.82	8.98	4.66	5.16 (0.001) (2.09, 8.24)	4.32 (0.007) (1.18, 7.47)	0.84 (0.566) (-2.04, 3.72)
Bodily Pain	12.09	12.06	5.87	6.22 (<.001) (4.01, 8.43)	6.19 (<.001) (3.94, 8.45)	0.03 (0.978) (-2.03, 2.09)
General Health	6.56	6.4	4.08	2.48 (0.028) (0.27, 4.69)	2.32 (0.045) (0.05, 4.59)	0.16 (0.878) (-1.92, 2.24)
Vitality	8.68	8.15	4.46	4.22 (<.001) (1.82, 6.61)	3.69 (0.003) (1.24, 6.14)	0.53 (0.646) (-1.72, 2.78)
Social Functioning	7.69	7.12	4.11	3.58 (0.013) (0.77, 6.4)	3.01 (0.041) (0.13, 5.9)	0.57 (0.670) (-2.06, 3.2)
Role Emotional	8.87	5.71	2.63	6.24 (0.002) (2.38, 10.1)	3.08 (0.126) (-0.87, 7.03)	3.16 (0.087) (-0.46, 6.78)
Mental Health	7.13	6.39	1.93	5.2 (<.001) (2.55, 7.85)	4.46 (0.001) (1.75, 7.17)	0.74 (0.558) (-1.75, 3.23)

Table 7. Change from Baseline SF-36 Components and Domains, Study 23

Param	Treatment (N)			Difference (p-value) (95% CI)		
	TIV8 (361)	TIV4 (373)	Pbo (360)	TIV8-Pbo	TIV4-Pbo	TIV8-TIV4
Physical Health CS	8.15	7.84	5.56	2.59 (0.001) (1.02, 4.16)	2.28 (0.004) (0.72, 3.84)	0.31 (0.668) (-1.1, 1.71)
Mental Health CS	4.18	3.23	2.84	1.35 (0.222) (-0.82, 3.51)	0.39 (0.721) (-1.76, 2.54)	0.95 (0.333) (-0.98, 2.88)
Physical Functioning	7.13	6.17	4.42	2.7 (0.002) (1.01, 4.39)	1.75 (0.041) (0.07, 3.43)	0.95 (0.212) (-0.55, 2.45)
Role Physical	7.48	7.41	5.91	1.57 (0.175) (-0.7, 3.85)	1.5 (0.195) (-0.77, 3.78)	0.07 (0.945) (-1.95, 2.1)
Bodily Pain	10.32	9.39	6.47	3.85 ($<.001$) (2.13, 5.58)	2.92 ($<.001$) (1.2, 4.64)	0.93 (0.231) (-0.59, 2.46)
General Health	4.96	4.23	2.8	2.15 (0.009) (0.55, 3.76)	1.42 (0.081) (-0.18, 3.02)	0.73 (0.315) (-0.7, 2.16)
Vitality	6.9	6.35	5.9	1 (0.277) (-0.8, 2.8)	0.45 (0.622) (-1.34, 2.25)	0.55 (0.500) (-1.04, 2.14)
Social Functioning	5.33	4.26	4.45	0.88 (0.425) (-1.29, 3.05)	-0.19 (0.864) (-2.35, 1.97)	1.07 (0.273) (-0.85, 2.99)
Role Emotional	5.41	4.5	3.64	1.77 (0.223) (-1.08, 4.61)	0.86 (0.552) (-1.97, 3.68)	0.91 (0.479) (-1.61, 3.43)
Mental Health	4.87	3.47	2.7	2.17 (0.030) (0.21, 4.14)	0.77 (0.441) (-1.19, 2.73)	1.4 (0.115) (-0.34, 3.14)

Table 8. Change from Baseline SF-36 Components and Domains, Study 24

Score	Treatment (N)		Difference (p-value) (95% CI) TIV8-Pbo
	TIV8 (248)	Pbo (240)	
Physical Health CS	9.78	7.77	2.01 (0.017) (0.37, 3.65)
Mental Health CS	6.77	4.81	1.96 (0.090) (-0.31, 4.23)
Physical Function	9.21	6.54	2.67 (0.007) (0.72, 4.63)
Role Physical	9.94	8.07	1.87 (0.115) (-0.46, 4.2)
Bodily Pain	12.78	10.56	2.23 (0.014) (0.45, 4)
General Health	4.85	4.06	0.79 (0.338) (-0.83, 2.41)
Vitality	9.78	6.23	3.55 (<.001) (1.54, 5.57)
Social Function	8.62	6.15	2.47 (0.025) (0.31, 4.62)
Role Emotional	6.90	6.17	0.73 (0.628) (-2.21, 3.66)
Mental Health	7.51	4.68	2.83 (0.014) (0.57, 5.08)

Table 9. Change from Baseline SF-36 Components and Domains, Study 62

Param	Treatment (N)			Difference (p-value) (95% CI)		
	TIV8 (147)	TIV4 (136)	Pbo (126)	TIV8-Pbo	TIV4-Pbo	TIV8-TIV4
Physical Health CS	8.02	7.09	2.22	5.8 (<.001) (2.68, 8.92)	4.87 (0.002) (1.81, 7.93)	0.93 (0.475) (-1.64, 3.51)
Mental Health CS	4.06	4.46	4.07	-0.01 (0.997) (-4.51, 4.5)	0.39 (0.863) (-4.03, 4.81)	-0.4 (0.833) (-4.12, 3.32)
Physical Functioning	6	5.58	1.43	4.57 (0.012) (1.04, 8.1)	4.15 (0.020) (0.66, 7.64)	0.42 (0.777) (-2.48, 3.31)
Role Physical	7.02	6.58	2.93	4.09 (0.057) (-0.13, 8.3)	3.65 (0.083) (-0.48, 7.79)	0.43 (0.805) (-3.03, 3.9)
Bodily Pain	11.26	8.41	4.92	6.34 (<.001) (3.31, 9.38)	3.49 (0.023) (0.48, 6.5)	2.86 (0.024) (0.38, 5.33)
General Health	4.62	4.21	0.89	3.73 (0.007) (1.02, 6.43)	3.33 (0.015) (0.65, 6.01)	0.4 (0.723) (-1.83, 2.63)
Vitality	8.42	7.01	4.1	4.32 (0.015) (0.83, 7.81)	2.91 (0.097) (-0.53, 6.36)	1.41 (0.331) (-1.44, 4.25)
Social Functioning	8.42	6.95	4.44	3.98 (0.048) (0.03, 7.93)	2.51 (0.209) (-1.41, 6.43)	1.48 (0.368) (-1.75, 4.7)
Role Emotional	3.42	4.11	2.86	0.57 (0.842) (-5.04, 6.17)	1.25 (0.657) (-4.3, 6.81)	-0.69 (0.766) (-5.25, 3.87)
Mental Health	4.31	3.73	2.97	1.34 (0.493) (-2.51, 5.19)	0.75 (0.697) (-3.05, 4.56)	0.59 (0.713) (-2.56, 3.73)

Table 10. Change from Baseline SF-36 Components and Domains, Study 63

Score	Treatment (N)		Difference (p-value) (95% CI) TIV8-Pbo
	TIV8 (752)	Pbo (370)	
Physical Health CS	8.87	4.08	4.79 (<.001) (3.64, 5.95)
Mental Health CS	5.31	2.26	3.05 (<.001) (1.51, 4.59)
Physical Function	7.02	3.08	3.94 (<.001) (2.65, 5.22)
Role Physical	8.72	3.68	5.04 (<.001) (3.53, 6.55)
Bodily Pain	11.72	5.75	5.97 (<.001) (4.71, 7.24)
General Health	5.49	2.63	2.86 (<.001) (1.76, 3.97)
Vitality	8.13	3.51	4.62 (<.001) (3.28, 5.96)
Social Function	7.11	2.31	4.8 (<.001) (3.24, 6.35)
Role Emotional	6.41	3.1	3.31 (0.002) (1.24, 5.38)
Mental Health	5.37	2.64	2.73 (<.001) (1.36, 4.1)

Table 11. Change from Baseline SF-36 Components and Domains, Study SC62

Score	Treatment (N)		Difference (p-value) (95% CI) TIV8-TSC
	TIV8 (563)	TSC (565)	
Physical Health CS	8.84	8.54	0.30 (.5) (-0.6, 1.2)
Mental Health CS	6.73	6.24	0.50 (.4) (-0.6, 1.59)
Physical Function	7.9	7.88	0.01 (.98) (-1.07, 1.1)
Role Physical	8.44	7.91	0.53 (.3) (-0.51, 1.56)
Bodily Pain	11.65	10.56	1.09 (.03) (0.09, 2.09)
General Health	6.48	6.13	0.35 (.5) (-0.55, 1.24)
Vitality	7.46	7.84	-0.38 (.5) (-1.4, 0.64)
Social Function	9.16	8.67	0.49 (.3) (-0.53, 1.52)
Role Emotional	7.93	7.07	0.86 (.2) (-0.47, 2.19)
Mental Health	6.38	5.91	0.47 (.4) (-0.57, 1.5)

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/s/

ROBERT ABUGOV
08/08/2016

GREGORY P LEVIN
08/16/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 125,276/ 125,472

Supporting document/s: SDN #732/ 78 (Supplement #107 and #018)
SDN #736/ 80 (Supplement #107 and #018)
SDN #759/ 86 (Supplement #107 and #018)

Applicant's letter date: November 24, 2015
December 7, 2015
January 31/ 29, 2016

CDER stamp date: November 24, 2015
December 7, 2015
February 1, 2016

Product: ACTEMRA[®] (tocilizumab)

Indication: Rheumatoid arthritis, polyarticular juvenile
idiopathic arthritis, and systemic juvenile
idiopathic arthritis

Applicant: Roche/Genentech Inc.

Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products

Reviewer: Brett Jones, PhD

Supervisor/Team Leader: Timothy Robison, PhD, DABT

Division Director: Badrul Chowdhury MD, PhD

Project Manager: Nina Ton, PharmD

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

ACTEMRA® (tocilizumab) is indicated for the treatment of: (1) moderately to severely active rheumatoid arthritis in adult patients who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs), 2) active polyarticular juvenile idiopathic arthritis in patients 2 years of age or older, and 3) active systemic juvenile idiopathic arthritis in patients 2 years of age or older.

The Sponsor submitted revised product labeling in the present supplement to comply with the Pregnancy and Lactation Labeling Rule (PLLR). No new nonclinical studies were provided in the supplement.

1.2 Brief Discussion of Nonclinical Findings

There is a complete nonclinical program for tocilizumab. No new nonclinical pharmacology or toxicology studies were submitted with this application. The nonclinical review of the proposed product label was limited to the Highlights of Prescribing Information (Use in Specific Populations), Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology). The Division of Pediatric and Maternal Health (DPMH) was consulted for the Highlights of Prescribing Information, Sections 8.1 (Pregnancy), and 8.2 (Lactation) in order to comply with the PLLR format. The revised labeling incorporates recommended changes provided by Dr. Christos Mastroyannis from DPMH. Below is the recommended text for the Highlights of Prescribing Information (Use in Specific Populations), Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology) after revisions to the Sponsor's proposed label.

1.3 Recommendations

Recommended labeling for the Highlights of Prescribing Information (Use in Specific Populations), Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology) is shown below. The revised labeling incorporates recommended changes provided by Dr. Christos Mastroyannis from DPMH. A detailed explanation of labeling changes is described later in the review. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

1.3.3 Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

2 Drug Information

2.1 Drug

Tradename: ACTEMRA®

Generic Name: Tocilizumab

Molecular Weight: 145 KDaltons

Pharmacologic Class: Recombinant, humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND (b) (4) IND (b) (4) IND (b) (4) and IND (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

ACTEMRA® (tocilizumab) is an IL-6 receptor antagonist indicated for the treatment of: (1) moderately to severely active RA in adult patients with who have had an inadequate response to one or more DMARDS, 2) active polyarticular juvenile idiopathic arthritis in patients ≥ 2 years old, and 3) active systemic juvenile idiopathic arthritis in patients ≥ 2 years old. The approved doses of ACTEMRA® for each indication are provided below.

2.7 Regulatory Background

ACTEMRA® (tocilizumab), an interleukin-6 (IL-6) receptor antagonist, was approved on January 8, 2010 for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients (Original-1). ACTEMRA® was approved on October 11, 2012 for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS) (Supplement-49). The approved adult intravenous (IV) starting dosage of ACTEMRA® (i.e., when used in combination with DMARDS or as monotherapy) is 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response. The approved adult subcutaneous (SC) dosage of ACTEMRA® in patients < 100 kg weight is 162 mg administered every other week, followed by an increase to every week based on clinical response. For adult patients ≥ 100 kg weight, the recommended SC dosage is 162 mg administered every week.

ACTEMRA® was approved on April 15, 2011 for the treatment of active systemic juvenile idiopathic arthritis in patients ≥ 2 years old (Supplement-22). The approved IV dose of ACTEMRA® for patients < 30 kg weight is 12 mg/kg administered every 2 weeks. For patients ≥ 30 kg weight, the approved dose is 8 mg/kg administered every 2 weeks.

ACTEMRA[®] was approved on April 29, 2013 for the treatment of active polyarticular juvenile idiopathic arthritis in patients ≥ 2 years old (Supplement-64). The approved IV dose of ACTEMRA[®] for patients < 30 kg weight is 10 mg/kg administered every 4 weeks. For patients ≥ 30 kg weight, the approved dose is 8 mg/kg administered every 4 weeks.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical studies were provided in the present supplement.

3.3 Previous Reviews Referenced

None.

11 Integrated Summary and Safety Evaluation

ACTEMRA[®] (tocilizumab) is indicated for the treatment of: (1) moderately to severely active RA in adult patients with who have had an inadequate response to one or more DMARDS, 2) active polyarticular juvenile idiopathic arthritis in patients ≥ 2 years old, and 3) active systemic juvenile idiopathic arthritis in patients ≥ 2 years old.

The Sponsor submitted revised product labeling in the present supplement to comply with the Pregnancy and Lactation Labeling Rule (PLLR). No new nonclinical studies were provided in the supplement.

The nonclinical review of the proposed product label was limited to the Highlights of Prescribing Information (Use in Specific Populations), Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology). The Division of Pediatric and Maternal Health (DPMH) was consulted for Sections 8.1 (Pregnancy), and 8.2 (Lactation) in order to comply with the PLLR format.

Nonclinical reproductive toxicology studies have been conducted with tocilizumab that include fertility and reproductive performance in mice (i.e., using a murine analogue of tocilizumab), embryofetal development in mice and monkeys, and pre- and post-natal development in mice.

In mice, a murine analogue of tocilizumab did not produce any functional impairment of the development and behavior, learning ability, immune competence, and fertility of offspring when dosed at 50 mg/kg intravenously with treatment every three days from implantation (GD 6) until post-partum day 21 (weaning). Fertility and reproductive performance were unaffected in male and female mice at intravenous doses up to 50 mg/kg administered every three days.

In monkeys, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at maternal intravenous doses of 10 and 50 mg/kg. There was no evidence for a teratogenic/dysmorphogenic effect up to 50 mg/kg.

The published literature suggests that IL-6 plays an important role in cervical dilatation and probably in placental delivery (Hassan et al., 2006; Osman et al., 2003; Tattersall et al., 2008; Törnblom et al., 2005). During the last trimester of pregnancy, IL-6 levels increase in parallel to circulating estrogen levels and IL-6 mRNA and protein increase significantly in cervix, myometrium, and chorio-decidua together with IL-1 β and IL-8. IL-6 has also been shown to be involved in the local process of inflammation occurring at parturition and enabling recruitment of leukocytes in the cervix and uterine wall in order to induce cervix ripening and dilatation and probably resorption of the interface between placenta and uterine wall (Hassan et al., 2006; Törnblom et al., 2005; Winkler, 2003). Inhibiting IL-6 signaling may therefore interfere with cervical ripening and dilatation, contractions and placenta delivery.

For mice deficient in IL-6 (Il6^{-/-} null mice), parturition was delayed relative to wild-type (Il6^{+/+}) mice (Robertson et al., 2010). Administration of recombinant IL-6 to Il6^{-/-} null mice restored the normal timing of delivery.

The carcinogenic potential of the IL-6 /IL-6 receptor (IL-6R) signaling pathway has been investigated in published scientific literature (Lu et al., 2006; Hideshima et al., 2007; Heikkila et al., 2008; Lippitz, 2013). The published literature suggests that IL-6/IL-6R signaling is tumor promoting. For example, IL-6 signaling via the IL-6R/gp130 complex and subsequent downstream activation of the JAK/STAT, MAPK, and PI3K/Akt pathways has been implicated in the tumorigenesis of multiple myeloma, ovarian cancer, lung cancer, bladder cancer, breast cancer, colon cancer, and prostate cancer (Bharti et al., 2016; Yao et al., 2013; Hideshima et al., 2001; Berishaj et al., 2007; Bharti et al., 2015). However, the literature also indicates that the IL-6 pathway may confer an anti-tumor role by supporting the adaptive immune response. In particular, IL-6 trans-signaling may be instrumental in facilitating anti-tumor T cell responses. IL-6 can support T-cell anti-tumor effects either at the lymph node or at the tumor microenvironment. For instance, acute activation of the IL-6/IL-6R pathway can influence the trafficking of lymphocytes to lymph nodes in order to induce their activation, proliferation, and polarization towards phenotypes that oppose the immunosuppressive tumor microenvironment.

In a targeted IL-6R null knockout mouse model, a decreased incidence of liver tumors following exposure to diethylnitrosamine (i.e., chemical which induces hepatocellular carcinoma) was observed. Knockout mice exposed to diethylnitrosamine exhibited increased hepatocyte apoptosis, decreased hepatocyte proliferation, and fewer (and smaller) hepatocellular carcinomas compared to wild-type mice. In contrast, mice fed a high fat diet and treated with diethylnitrosamine displayed normal liver apoptosis and hepatocellular carcinoma development.

No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab. The malignancy risk in humans from an antibody that disrupts signaling through the IL-6 receptor, such as tocilizumab, is unknown.

Labeling Review:

Below is the recommended text for the Highlights of Prescribing Information (Use in Specific Populations), Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology) after revisions to the Sponsor's proposed label. The revised labeling incorporates recommended changes provided by Dr. Christos Mastroyannis from DPMH. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

Labeling was updated to match current practices for the Pregnancy and Lactation Labeling Rule.

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

(b) (4)

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

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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/s/

BRETT R JONES
08/11/2016

TIMOTHY W ROBISON
08/11/2016
I concur

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s018

OTHER REVIEW(S)



Division of Pediatric and
Maternal Health
Office of New Drugs
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PLLR Labeling Memorandum

Date: 7/15/2016 **Date consulted:** 1/7/2016

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Drug: ACTEMRA® (tocilizumab) for intravenous or subcutaneous injection

BLA: 125276/S-0107
125472/S-018

Applicant: Genentech, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication(s): 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 had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

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.

Materials Reviewed:

- DPMH consult request dated January 7, 2016 in DARRTS.
Reference ID: 3870402
- November 24, 2015, package insert submitted by applicant.
- Applicant's response to information request (IR) by the Division on January 13, 2016, dated January 28, 2016.
Reference ID: 3872644
- DPMH review of Actemra labeling of August 23, 2013
Reference ID: 3362010

Consult Question:

DPARP requests that DPMH review the labeling content and format for the requirements of Pregnancy & Lactation Labeling Rule (PLLR).

REGULATORY HISTORY

On November 24, 2015, Genentech submitted two efficacy supplements for Biologics License Application (BLA) 125276/S-107 and BLA 125472/S-018 to add health-related outcomes assessed by the Short Form Health Survey (SF-36) to sections 14.1 and 14.2 of Actemra (Tocilizumab) labeling. Because these supplements were submitted after June 30, 2015, labeling will be converted to the PLLR format.

- Actemra (BLA 125276) for intravenous infusion was approved in the U.S. on January 8, 2010, and is indicated for the treatment of rheumatoid arthritis. BLA 125276 included a Post-Marketing Requirement (PMR) for a pregnancy exposure registry.
- Actemra (BLA 125472) for subcutaneous injection was approved in the U.S. on October 21, 2013, and is indicated for the treatment of RA, Polyarticular Juvenile Idiopathic Arthritis (PJIA) and Systemic Juvenile Idiopathic Arthritis (SJIA).

BACKGROUND

Drug Characteristics

Actemra is a recombinant, interleukin 6 (IL-6) receptor monoclonal antibody. Actemra inhibits IL-6-mediated signaling through receptors by binding specifically to soluble and membrane-bound IL-6 receptors. IL-6 is involved in T cell activation, induction of immunoglobulin secretion and initiation of hepatic acute phase protein synthesis. In addition, IL-6 plays a role in the inflammatory processes such as those that occur in rheumatoid arthritis through the production of IL-6 by synovial and endothelial cells leading to the local production of IL-6 in joints affected by the inflammatory process.

The molecular weight is 148,000 Daltons. The median half-life is about four days. 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.¹

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

Rheumatoid arthritis (RA) and pregnancy

Rheumatoid arthritis is a chronic, autoimmune disease that affects more women than men and usually manifests between the ages of 30 to 50.² Management of RA can be challenging in pregnant women. While some women experience an improvement in RA symptoms during pregnancy many others require continuous medication management.¹ The reader is referred to the previous DPMH review of Actemra by Carrie Ceresa, PharmD, MPH for further details regarding RA and pregnancy³ and to a consult review by Miriam Dinatale, DO on Humira (March 24,2016) another monoclonal antibody that binds to TNF-alpha(a) for the treatment of rheumatoid arthritis.

Current State of Actemra Labeling

Actemra was previously reviewed by DPMH on August 23, 2013, and labeling is currently in the “PLLR hybrid” format because the final rule had not yet been published but the applicant was willing to comply with the components that would be required under PLLR. Currently approved Pregnancy labeling includes information on the Actemra pregnancy registry and nonclinical data. No human data are included.

Nursing Mothers labeling notes that it is not known if tocilizumab is absorbed systemically after ingestion [REDACTED]^{(b) (4)} IgG is excreted in human milk, it is expected that tocilizumab could be present in human milk. Current labeling recommends that either the drug or nursing be discontinued.

¹ Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. *Am J Gastroenterol.* 2013;108:1426-38.

² Al-Shakarchi, I., Gullick, N., Scott, D. (2013). Current perspectives on tocilizumab for the treatment of rheumatoid arthritis: a review. *Patient Preference and Adherence*,7:653-666.

³ DPMH review. Actemra (tocilizumab) subcutaneous injection. BLA 125472. August 23, 2013. Reference ID 3362010

The current review provides suggested revisions and structuring of existing information related to the Pregnancy and Lactation labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

DATA REVIEW

Pregnancy

Nonclinical Experience

Currently approved Actemra labeling includes data from pregnant cynomolgus monkeys who were administered intravenous tocilizumab during organogenesis at doses 1.25 times the maximum recommended human dose (MRHD), which resulted in embryo-fetal death. The reader is referred to the nonclinical reviewed by Brett Jones, PhD for further details.

Literature Review

The applicant conducted a literature search to identify publications of use of Actemra during pregnancy and its effects on pregnancy outcomes. This reviewer also searched PubMed, Embase, ReproTox and TERIS data bases. A review of literature is provided below.

There are limited data available regarding the use of tocilizumab during pregnancy.^{4,5} According to a 2014 review article, human experience with tocilizumab during pregnancy was documented mainly in conference abstracts, with the outcomes of 31 pregnancies reported at one annual meeting in 2010⁶. Those outcomes included

- 13 elective terminations,
- 7 spontaneous abortions (5 also received methotrexate), and
- 11 full-term newborns (9 also received methotrexate).

Of the full-term deliveries, (mothers had received 8 mg/kg tocilizumab).

- 10 infants were healthy
- one died at 3 days of age from complications of placenta previa.

In a retrospective study conducted in Japan, (Nakajima, *et al.*)⁷, 61 pregnant women were exposed to tocilizumab at conception. There were no increased rates of spontaneous abortions or congenital abnormalities in patients with rheumatic disease who were taking tocilizumab (see Table 1).

⁴ Calligaro A, Hoxha A, Ruffatti A, Punzi L. Are biological drugs safe in pregnancy? *Reumatismo*. 2015 Mar 31; 66(4): 304-17.

⁵ Østensen M: Safety issues of biologics in pregnant patients with rheumatic diseases. *Current Opinion in Rheumatology* 2011, 23:293–298. *Ann. N.Y. Acad. Sci.* 1317 (2014) 32–38.

⁶ Hyrich KL, Verstappen SMM. 2014. Biologic therapies and pregnancy: the story so far. *Rheumatology* 53:1377-1385.

⁷ Nakajima K, Watanabe O, Mochizuki M et al. Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. *Mod Rheumatol*. 2016;1-17

Table 1: Outcomes of Pregnancies Exposed to Tocilizumab, Retrospective Study in Japan †

Pregnancies	N=61
Reported outcomes	N=50
Normal births (no congenital anomalies)	36 (72%)*
Low birth weight(<2500)	5
Neonatal asphyxia	1
Spontaneous Abortion	9 (18%)*
Elective Abortions	5 (10%)*
Caudal Regression Syndrome	1

*Percentages are calculated as number of cases per number of reported outcomes (n=50)

†From Nakajima et.al. 2016.

Review of Pharmacovigilance Database

The applicant conducted a search of its Global Safety Database to identify all pregnancy cases with maternal or paternal exposure to Actemra using the MedDRA 18.0 Pregnancy and neonatal topics (SMQ) up to October 10, 2015

The applicant identified 661 pregnancy related cases. Of these pregnancy cases, 632 concerned exposed mothers and 29 concerned exposed fathers. In one case, the parental exposure was not reported.

For cases with maternal exposure (n=632), pregnancy outcomes were not available for 270 cases (43%). The remaining 362 maternal exposure cases (57%) represent cases for which pregnancy outcomes are available (retrospective 137, prospective 224)⁸.

Of the 137 retrospective pregnancy cases concerning maternal exposure, the pregnancy outcome was reported as:

- live birth (N=72 [53%]),
- ectopic pregnancy (N=1 [< 1%]),
- spontaneous abortion (N=38 [28%]),
- therapeutic abortion (N=24 [18%]), and
- still birth (N=2 [1%]).

Of the 224 prospective cases concerning maternal exposure the pregnancy outcome was:

- live birth (N=142 [63%]),
- ectopic pregnancy (N=3 [1%]),
- spontaneous abortion (N=39 [17%]),
- therapeutic abortion (N=39 [17%]) and
- still birth (N=1 [<1%]).

⁸ Reports were regarded as prospective if the pregnancy outcome was not known at the time of receipt, by Roche, of the initial report; reports were regarded as retrospective if the outcome was known at the time of reporting.

Table 2: Pregnancy Outcomes with Paternal Exposure*

Paternal exposure (N=29)	
Known outcome N=17 (59%)	Unknown outcome N=12 (41%)
Live birth n=13 (76%)	
Normal birth n=12 (71%)	
Abnormal birth n=1 (6%)**	
Spontaneous abortions n=3 (18%)	
Therapeutic (elective) abortion n=1 (6%)	

**Premature rupture of membranes

*From applicant's pharmacovigilance database

From the 362 maternal and 29 paternal exposures with known outcomes, the total adverse birth outcomes identified by the Congenital, familial and genetic disorders SMQ included 11 cases with frequency of one for each abnormality (congenital pyelocaliectasis, polydactyly, anorectal agenesis, caudal regression syndrome, developmental hip dysplasia, ventricular septal defect, premature baby, prematurity (premature baby)-esophageal atresia- interarticular communication, chromosomal abnormalities, ventricular septal defect, microcephaly). The incidence of the reported abnormalities are approximately 3% (11 of 391).

Pregnancy Exposure Registry.

The Actemra pregnancy exposure registry is a PMR for original Actemra BLA 125276, approved on January 8, 2010. It is a U.S.-based registry designed to monitor planned or unplanned pregnancies exposed to Actemra (tocilizumab) when the drug is used to treat rheumatoid arthritis (RA). The target study completion is planned for December 31, 2016 with a final report submission, December 31, 2017. It was anticipated that approximately 20 pregnant women with exposure to Actemra could be enrolled in the Registry each year, for a planned duration of five years in order to achieve recruitment of 100 patients per arm. As of December 31, 2015, only 11 Actemra-exposed patients have been enrolled. No interim report is provided. The applicant is interested to engage the Agency later in 2016 to discuss plans given that the registry enrollment has remained low.

Summary

This reviewer agrees with the applicant's conclusion that the prospective spontaneous abortion incidence proportion of 17.4% is consistent with the background rate of 15-20% pregnancy loss in the general population. Pregnancy loss in RA population is higher (24-33%).⁹ There is no specific pattern for abnormalities. The incidence of the reported abnormalities are approximately 3%. Published rates for any congenital abnormalities in the RA population have been reported to be 4.25%.¹⁰ From the above findings, there is

⁹ Verstappen, SMM, King, Y, Watson, K, Symmons, DPM, Hyrich, K. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011; 70:823-826.

¹⁰ Nørgaard M, Larsson H, Pedersen L, Granath F, Askling J, Kieler H, Ekblom A, Sørensen HT,

no safety signal that warrants any further evaluation, therefore, no specific language regarding congenital abnormalities or spontaneous abortion will be added to the labeling at this time. The labeling should be updated upon completion of the ongoing Actemra pregnancy exposure registry study.

Lactation

Nonclinical Experience

There were no animal lactation studies that were conducted.

Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*¹¹, the Drugs and Lactation Database (LactMed),¹² Micromedex¹³, and of published literature in PubMed and Embase using the search terms “tocilizumab and lactation” and “tocilizumab and breastfeeding.” A review of published literature is provided below.

In the retrospective study (Nakajima, *et al.*) that was reviewed above, two out of 36 women resumed tocilizumab during lactation. There were no subsequent adverse events reported in newborns.⁶

In *Medications and Mother's Milk*, Thomas Hale, a breastfeeding expert, states the following regarding tocilizumab use during lactation:

“Tocilizumab has a large molecular weight of 148 kilodaltons and is unlikely to pass into breast milk”.

LactMed states the following: “Because tocilizumab is a large protein molecule with a molecular weight of about 148,000, the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract.” Lactmed further recommends that “if tocilizumab is required by the mother, it is not a reason to discontinue breastfeeding.”¹⁴

Micromedex notes the following; “Infant risk cannot be ruled out.” There is no published information regarding tocilizumab drug levels in human milk, the effects of the drug in breastfed infants or the effects of the drug on milk production.

Stephansson O. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. *J Intern Med.* 2010 Oct;268(4):329-37.

¹¹ Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 422-423.

¹² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹³ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 7/1/16.

¹⁴ Gotestam Skorpen C, Hoeltzenbein M, Tincani A et al. The EULAR points to consider for use of anti-rheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016;75:795-810.

Summary

There are no data on the presence of tocilizumab in human milk. Some serious adverse reactions which have been observed with Actemra treatment in the clinical trials with adult and pediatric population include: serious infections, neutropenia, thrombocytopenia and elevated liver enzymes. However, tocilizumab is a large protein molecule that is most likely degraded in the gastrointestinal tract. DPMH concurs that available data do not suggest a risk associated with the use of tocilizumab during lactation; however available data are extremely limited (2 partial case reports), and insufficient to characterize the safety of tocilizumab use during lactation. Therefore, DPMH recommends that the following risk/benefit statement is included in section 8.2 of labeling:

The lack of clinical data during lactation precludes clear determination of the risk of ACTEMRA to an infant during lactation; therefore, the development and health benefits of breastfeeding should be considered along with the mother's clinical need for ACTEMRA and any potential adverse effects on the breastfed infant from ACTEMRA or from the underlying maternal

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In animal fertility studies conducted in male and female mice administered intravenous tocilizumab at doses of 50mg/kg every three days, there was no evidence of impaired fertility. The reader is referred to the nonclinical review by Brett Jones, PhD for further details.

Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding tocilizumab and its effects on fertility and found no relevant literature.

Summary

Animal fertility studies of administration of tocilizumab did not show any adverse effects on fertility. Since there are no human data available on the effect of tocilizumab on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in Actemra labeling.

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of Actemra labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
 - The "Pregnancy" section of Actemra labeling was formatted in the PLLR format to include: "Pregnancy Exposure Registry," "Risk Summary," "Clinical Considerations," and "Data" sections.
- **Lactation, Section 8.2**
 - The "Lactation" section of Actemra labeling was formatted in the PLLR format to include: the "Risk Summary" section.
- **Patient Counseling Information, Section 17**

The “Patient Counseling Information” section of labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of Actemra labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on July 26, 2016. DPMH refers to the final NDA action for final labeling.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHRISTOS MASTROYANNIS
08/10/2016

TAMARA N JOHNSON
08/10/2016

LYNNE P YAO
08/12/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 5, 2016

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 - ACTEMRA (tocilizumab)
Solution for intravenous infusion
Solution for subcutaneous injection (Actemra)

Reference is made to DPARP's consult request dated January 7, 2016, requesting review of the proposed Package Insert (PI) and Medication Guide (MG) for ACTEMRA (tocilizumab) Solution for intravenous infusion, Solution for subcutaneous injection (Actemra).

OPDP has reviewed the proposed PI and MG entitled, "Actemra SCPI 8-3-16.doc" that was sent via e-mail from DPARP to OPDP on August 3, 2016. OPDP comments are provided directly on the attached copy of the 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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/s/

ADEWALE A ADELEYE
08/05/2016