

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125276Orig1s064

Trade Name: Actemra

Generic Name: tocilizumab

Sponsor: Genentech, Inc.

Approval Date: April 29, 2013

This Prior Approval supplemental biologics application provides for the use of Actemra (tocilizumab) for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older and a proposed modification to the approved REMS.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

APPROVAL LETTER



BLA 125276/64

**SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT
NEW POSTMARKETING REQUIREMENT**

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

Attention: Stuart Heminway
Program Director, Regulatory Affairs

Dear Mr. Heminway:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 28, 2012, received June 29, 2012, submitted under section 351(a) of the Public Health Service Act for Actemra (tocilizumab).

We acknowledge receipt of your amendments dated August 27, September 12 and 27, and October 24 (2), 2012, and January 18, April 3, 15, 19, and 23, 2013. The April 23, 2013 submission comprised an assessment of your risk evaluation and mitigation strategy (REMS), required with submission of your sBLA for a new indication for use.

This Prior Approval supplemental biologics application provides for the use of Actemra (tocilizumab) for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older and a proposed modification to the approved REMS.

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

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, 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 includes 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 28, 2012, submission containing final printed carton and container labels.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. Approval of this submission by FDA is not required before the labeling is used.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

This supplement also addresses the required pediatric assessment for the following postmarketing requirement listed in the January 8, 2010, approval letter for BLA 125276/0.

- 1 Assessment of pharmacokinetic (PK/PD) parameters and dosing, efficacy, safety, tolerance and immunogenicity in the pediatric population ages ≥ 2 years to < 17 years with polyarticular JIA.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the January 8, 2010, and April 15, 2011 approval letters that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Actemra (tocilizumab) was approved on January 8, 2010, for adults with rheumatoid arthritis (RA). Data from the adult RA clinical trials showed an association between Actemra (tocilizumab) treatment and the risks of serious infection, gastrointestinal perforation, and the potential for malignancy. Since Actemra (tocilizumab) was approved, we have become aware of events of serious infections in clinical trials of pediatric patients with polyarticular JIA (pJIA). The pediatric clinical trials in patients with pJIA comprise a relatively limited safety database, therefore the risks of serious infection, gastrointestinal perforation, and malignancy need to be defined in this pediatric population. In addition, since the long-term risks of Actemra (tocilizumab) in pediatric patients with pJIA are unknown and these patients will require chronic treatment, further investigation of the long-term safety of Actemra (tocilizumab) is essential. We are also aware of literature suggesting that IL6 has important functions on the developing musculoskeletal system, raising concern regarding effects on growth in pJIA patients with Actemra (tocilizumab). We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known risk of serious infections and gastrointestinal perforations and the unexpected serious risk of malignancy and effects on growth with Actemra (tocilizumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1 A long-term safety study in 400 pediatric patients 2-17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of 400 pediatric pJIA patients treated with other biologics as standard of care. Patients should be followed for 5 years.

The timetable you submitted on April 15, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	February 2014
Study Completion:	September 2022
Final Report Submission:	April 2023

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol to your IND 11972, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Actemra (tocilizumab) was originally approved on January 8, 2010, with the most recent REMS modification approved on October 11, 2012. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of the addition of information in the appended REMS materials, specifically the Dear Healthcare Professional letter and the journal information pieces, to describe the new indication for the use of Actemra (tocilizumab) in polyarticular JIA patients.

Your proposed modified REMS, submitted on June 28, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on January 8, 2010.

There are no changes to the REMS assessment plan described in our June 20, 2012, letter.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125276 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

BLA 125276 REMS ASSESSMENT

**NEW SUPPLEMENT FOR BLA 125276
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125276
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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:

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

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. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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 Philantha Bowen, Senior Regulatory Project Management Officer, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

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

/s/

SALLY M SEYMOUR
04/29/2013
for Badrul Chowdhury

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ACTEMRA® (tocilizumab) Injection, for intravenous infusion

Initial U.S. Approval: 2010

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

Indications and Usage (1.)	10/2012
Indications and Usage (1.2)	04/2013
Dosage and Administration (2.1)	10/2012
Dosage and Administration (2.2, 2.4, 2.5)	04/2013
Warnings and Precautions (5.3)	04/2013
Warnings and Precautions (5.5)	10/2012
Warnings and Precautions (5.8)	04/2013

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.

Rheumatoid Arthritis (2.1)

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.

Polyarticular Juvenile Idiopathic Arthritis (2.2)

Recommended 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 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 (2.4)

- 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.

Dose Modifications (2.5)

- 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):

- 80 mg per 4 mL (3)
- 200 mg per 10 mL (3)
- 400 mg per 20 mL (3)

CONTRAINDICATIONS

- ACTEMRA should not be administered to 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. (2.5, 5.3)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.5)
- Live vaccines – should not be given 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. (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. Pregnancy registry available. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2013

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WARNING: RISK OF SERIOUS INFECTIONS

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

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

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

Reported infections include:

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

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

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

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis (RA)

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

1.2 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 DMARDs. The recommended dose 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 (2.5)*, *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)*].

2.2 Polyarticular Juvenile Idiopathic Arthritis

ACTEMRA may be used alone or in combination with methotrexate. The recommended dose of ACTEMRA for PJIA patients given once every 4 weeks as a 60-minute single intravenous drip infusion is:

Recommended 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

- A change in dose should not be made 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 (2.5)*].

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 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

- A change in dose should not be made 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 (2.5)*].

2.4 General Considerations for Administration

- ACTEMRA has not been studied and its use should be avoided 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.
- 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).

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

- PJIA and SJIA patients **less than 30 kg**: utilize a **50 mL** infusion bag or bottle, then follow steps 1 and 2 below.
- Adult Rheumatoid Arthritis, PJIA and SJIA patients **at or above 30 kg weight**: utilize a **100 mL** infusion bag or bottle, then follow steps 1 and 2 below.
 - Step 1. Withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA injection required for the patient’s dose from the infusion bag or bottle.
 - Step 2. Slowly add ACTEMRA for intravenous infusion from each vial into the 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.

2.5 Dosage Modifications

ACTEMRA treatment should be interrupted 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	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg per kg or interrupt ACTEMRA until ALT or AST have normalized
Greater than 3 to 5x ULN (confirmed by repeat testing)	Interrupt 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	Interrupt ACTEMRA dosing When ANC greater than 1000 cells per mm ³ resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg 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	Interrupt ACTEMRA dosing When platelet count is greater than 100,000 cells per mm ³ resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg 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, concomitant methotrexate and/or other medications should be dose modified or stopped and ACTEMRA dosing interrupted 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):

- 80 mg per 4 mL
- 200 mg per 10 mL
- 400 mg per 20 mL

4 CONTRAINDICATIONS

ACTEMRA should not be administered to 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.

ACTEMRA should not be administered 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.

Patients should be closely monitored 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)].*

ACTEMRA should be interrupted 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, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Tuberculosis

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ACTEMRA.

Anti-tuberculosis therapy should also be considered 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.

Patients should be closely monitored 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. ACTEMRA should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation [*see Adverse Reactions (6.1)].*

5.3 Laboratory Parameters

Rheumatoid Arthritis

Neutrophils

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.
- Neutrophils should be monitored every 4 to 8 weeks [see *Clinical Pharmacology (12.2)*]. For recommended modifications based on ANC results see [Dosage and Administration (2.5)].

Platelets

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)*].

- 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.
- Platelets should be monitored every 4 to 8 weeks. For recommended modifications based on platelet counts see [Dosage and Administration (2.5)].

Liver Function Tests

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)*]. 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.
- ALT and AST levels should be monitored every 4 to 8 weeks. When clinically indicated, other liver function tests such as bilirubin should be considered. For recommended modifications based on transaminases see [Dosage and Administration (2.5)].

Lipids

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)*].

- Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.
- Patients should be managed 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. Neutrophils, Platelets, ALT and AST should be monitored at the time of the second infusion and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA. Lipids should be monitored as above for RA [see *Dosage and Administration (2.4)*].

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 and death, have been reported in association with infusion of ACTEMRA [see *Adverse Reactions (6.1, 6.2)*]. 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, and in 0.2% (8 out of 4009) of patients in the all-exposure rheumatoid arthritis population; and in the SJIA controlled trial, 1 out of 112 patients (0.9%). In the postmarketing setting, events of clinically significant hypersensitivity and anaphylaxis, including events with a fatal outcome, have occurred in patients treated with a range of doses of ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Clinically significant hypersensitivity and anaphylaxis events have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA [see *Adverse Reactions (6.2)*]. ACTEMRA should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis. If anaphylaxis or other clinically significant hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately and ACTEMRA should be permanently discontinued. 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. Patients should be closely monitored 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

Live vaccines should not be given 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

6.1 Clinical Trials Experience

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.

Rheumatoid Arthritis

The ACTEMRA data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA 8 mg per kg monotherapy (288 patients), ACTEMRA 8 mg per kg in combination with DMARDs (including methotrexate) (1582 patients), or ACTEMRA 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. 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 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 and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of ACTEMRA 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 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 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 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 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 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 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 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 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

Clinically significant hypersensitivity reactions, including anaphylaxis associated with ACTEMRA and requiring treatment discontinuation 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. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction [see *Warnings and Precautions (5.5)*].

Laboratory Tests

Neutrophils

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 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 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)*].

Platelets

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 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)*].

Liver Function Tests

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, or reduction in ACTEMRA 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	Methotrexate	ACTEMRA 4 mg per kg + DMARDs	ACTEMRA 8 mg per kg + DMARDs	Placebo + DMARDs
	N = 288 (%)	N = 284 (%)	N = 774 (%)	N = 1582 (%)	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 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, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA 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 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 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

Polyarticular Juvenile Idiopathic Arthritis

The safety of ACTEMRA 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 all exposure population (defined as patients who received at least one dose of ACTEMRA) 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)*].

Infections

The rate of infections in the ACTEMRA 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 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)*].

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 Tests

Neutrophils

During routine laboratory monitoring in the ACTEMRA 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.

Platelets

During routine laboratory monitoring in the ACTEMRA 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.

Liver Function Tests

During routine laboratory monitoring in the ACTEMRA 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%).

Systemic Juvenile Idiopathic Arthritis

The data described below reflect exposure to ACTEMRA 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 (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 in the open-label extension phase.

The most common adverse events (at least 5%) seen in ACTEMRA 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 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 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. One patient in the placebo group escaped to ACTEMRA 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 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 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 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 treatment group and 5% of patients in the placebo group experienced an event. In the ACTEMRA 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 during the controlled and open label extension study [see Warnings (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 Tests

Neutrophils

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

Platelets

During routine monitoring in the 12 week controlled phase, 1% of patients in the ACTEMRA 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 group, with no associated bleeding.

Liver Function Tests

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 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 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 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 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.

6.2 Postmarketing Experience

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

- Fatal anaphylaxis [*see Warnings and Precautions (5.5)*]

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 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, therapeutic monitoring of 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. Prescribers should exercise caution when ACTEMRA is coadministered 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

Live vaccines should not be given concurrently with ACTEMRA [see *Warnings and Precautions (5.8)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg per kg from gestation day 20-50) during organogenesis. 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 10 mg per kg and 50 mg per kg doses (1.25 and 6.25 times the human dose of 8 mg per kg every 2 to 4 weeks based on a mg per kg comparison).

Nonteratogenic Effects. 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 per kg intravenously with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Pregnancy Registry: To monitor the outcomes of pregnant women exposed to ACTEMRA, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether tocilizumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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. 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. 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 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 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).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab binds specifically 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 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 both doses, however the greatest improvements were observed with 8 mg per kg ACTEMRA. Pharmacodynamic changes were also observed to occur after ACTEMRA administration in PJA and SJA 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, 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

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)*].

Polyarticular Juvenile Idiopathic Arthritis

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

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.

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. 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.

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.

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

Carcinogenesis. No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab.

Mutagenesis. Tocilizumab was negative in the in vitro Ames bacterial reverse mutation assay and the in vitro chromosomal aberrations assay using human peripheral blood lymphocytes.

Impairment of Fertility. Fertility studies conducted in male and female mice using a murine analogue of tocilizumab showed no impairment of fertility.

14 CLINICAL STUDIES

Rheumatoid Arthritis

The efficacy and safety of 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 ACTEMRA-treated patients achieving ACR 20, 50 and 70 responses are shown in **Table 3**. In all 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 (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	N/A
ACR 50													
Week 24	34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
Week 52	N/A	N/A	10%	29% (0.14, 0.25)	36% (0.21, 0.32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 70													
Week 24	15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
Week 52	N/A	N/A	4%	16% (0.08, 0.17)	20% (0.12, 0.21)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Major Clinical Responses^b													
Week 52	N/A	N/A	1%	4% (0.01, 0.06)	7% (0.03, 0.09)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

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

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

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

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

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

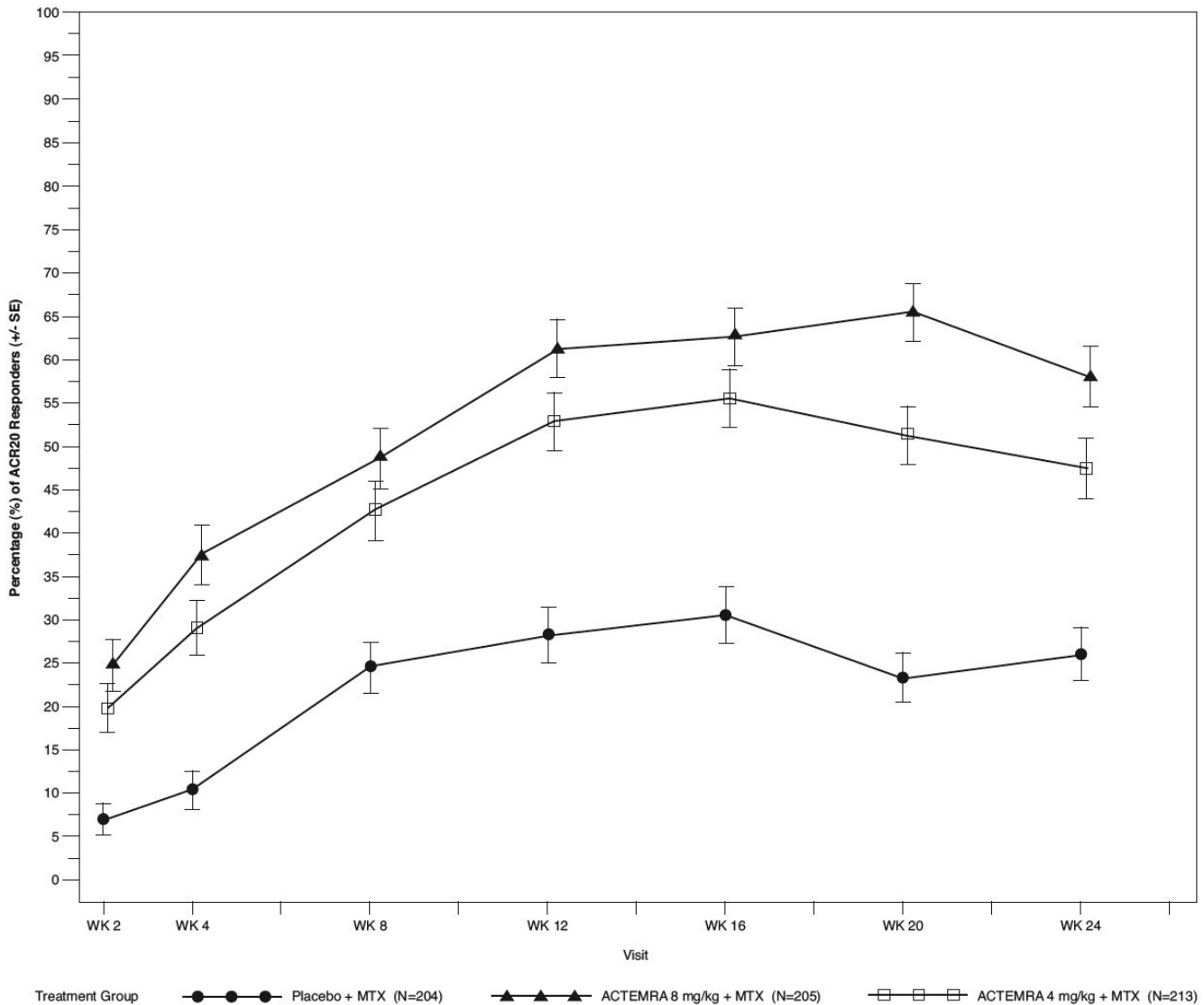
^a Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

^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 responses 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.

Polyarticular Juvenile Idiopathic Arthritis

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.

Systemic Juvenile Idiopathic Arthritis

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

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

Storage and Stability: Do not use beyond expiration date on the container. ACTEMRA must be refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect the vials from light by storage in the original package until time of use. 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

Patients and parents or guardians of minors with PJIA or SJIA should be advised 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.

MEDICATION GUIDE
ACTEMRA® (AC-TEM-RA)
(tocilizumab)

Read this Medication Guide before you start ACTEMRA and before each infusion. 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 such as:
 - fever, 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 and every 4 to 8 weeks for rheumatoid arthritis (RA) and Polyarticular Juvenile Idiopathic Arthritis (PJIA) and every 2 to 4 weeks for Systemic Juvenile Idiopathic Arthritis (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.

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. Normal cholesterol levels are important to good heart health.

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) and systemic juvenile idiopathic arthritis (SJIA) ages 2 and above.

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. 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?

- You will receive ACTEMRA from a healthcare provider through a needle placed in a vein in your arm (IV or intravenous infusion). The infusion will take about 1 hour to give you the full dose of medicine.
- For rheumatoid arthritis you will receive a dose of ACTEMRA about every 4 weeks.
- For PJIJA 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.

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. This happens with other biologic medicines used to treat RA. 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 of ACTEMRA, even if they did not occur with an earlier infusion. Tell your healthcare provider right away if you have any of the following signs of a serious allergic reaction:
 - shortness of breath or trouble breathing
 - skin rash
 - swelling of the lips, tongue, or face
 - chest pain
 - feeling dizzy or faint
- **Nervous system problems.** Multiple Sclerosis has been diagnosed rarely 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)

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: sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate.

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

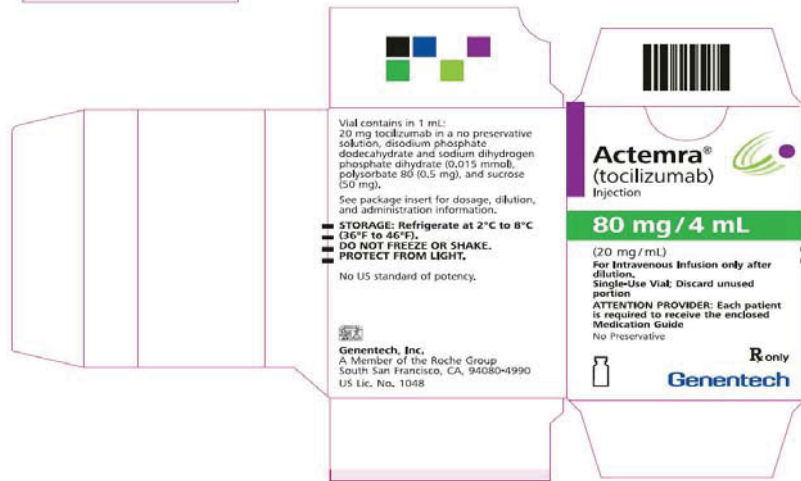
MG Revised: April 2013

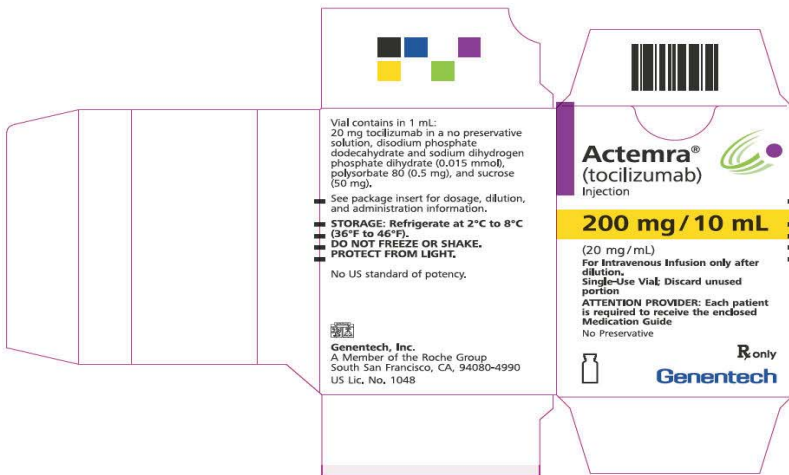
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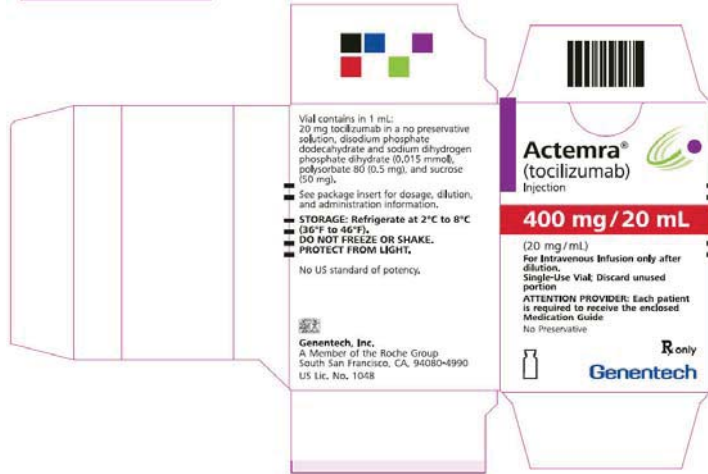
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Initial REMS Approved: 01/08/2010

Most Recent Modification: 04/29/2012

BLA 125276 ACTEMRA[®] (tocilizumab)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080

I. GOALS

The goal of the ACTEMRA REMS is:

- To inform healthcare providers about the serious risks associated with ACTEMRA.

II. REMS ELEMENTS

A. Communication Plan (FDCA Section 505-1(e)(3))

In accordance with FDCA 505-1(e)(3), Genentech, A Member of the Roche Group, will implement a communication plan to the following adult and pediatric healthcare providers:

- Rheumatologists and rheumatology healthcare providers who are likely to prescribe ACTEMRA
- Infectious disease specialists who may be consulted about serious infection
- Gastroenterologists and hepatologists who may be consulted about gastrointestinal perforation, hepatic disease, or hepatic impairment
- Family practitioners, general practitioners, osteopaths, internists, and internal medicine specialists who may be consulted about serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with ACTEMRA
- Emergency medicine specialists who may treat serious infections, gastrointestinal perforations, and changes in liver function
- Neurologists who may treat demyelinating disorders
- Oncologists who may treat malignancies

Elements of the communication plan include the following:

1. A Dear Healthcare Provider Letter (see **Attachment A**) will be distributed to adult and pediatric prescribers to include rheumatologists, gastroenterologists, hepatologists, neurologists, oncologists, infectious disease specialists, family medicine specialists, internal medicine specialists, emergency medicine specialists, and to infusion sites. This letter will be distributed within 60 days of approval of a new indication.

A Professional Label that includes the Medication Guide will also be distributed in this communication.

2. Prescriber Education Slide Deck

The prescriber education slide deck will provide information about specific safety risks (demyelination, malignancy, lipid elevations and monitoring advice) associated with ACTEMRA.

The slides will be available within 60 days of REMS modification approval through the following distribution methods:

- The www. ACTEMRAREMS.com website (see **Attachment J** for the REMS Website landing page screenshot)
- Genentech Rheumatology Medical Science Liaison (MSL) will conduct educational sessions presenting these slides to rheumatology prescribers of ACTEMRA.
- Hard copy mailing, upon request, through Genentech's toll-free medical information line (1-800-228-3672)

The prescriber education slide deck will be available for 3 years following approval of the REMS Modification. The prescriber education slide deck is appended to this document (see **Attachment B**)

3. Dissemination of information about the known and potential risks associated with ACTEMRA to healthcare providers through certain professional societies' scientific meetings and journals:
 - a) For display as a panel/poster and distribution as printed material at major convention meetings of rheumatologists and other healthcare professionals specializing in rheumatology where the company has a sponsored booth for 2 years following product approval.
 - b) For quarterly presentation as a printed information piece in *Arthritis and Rheumatism*, *The Rheumatologist*, *Clinical Infectious Diseases*, *Clinical Gastroenterology and Hepatology*, *American Family Physician*, *Annals of Internal Medicine*, *Annals of Emergency Medicine*, *Neurology*, *Pediatrics*, *AAP (American Academy of Pediatrics) News*, and *Infectious Diseases in Children* for 3 years following product approval.
 - c) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years following product approval.

The REMS journal information pieces are appended to this document (see **Attachments C, D, E, F, G, H and I**).

4. Genentech will ensure that all materials listed in or appended to the ACTEMRA REMS program will be available through the ACTEMRA REMS program website www.ACTEMRAREMS.com or by calling 1-800-228-3672. The ACTEMRA REMS program website will exist for 3 years following approval of the REMS Modification. The landing page for the ACTEMRA REMS program website is appended to this document (see **Attachment J**).

B. Timetable for Submission of Assessments

REMS assessments will be submitted to FDA at 18 months, 3 years, and 7 years after approval of the original REMS (January 8, 2010). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date so that it will be received by the FDA on or before the due date.

ATTACHMENT A: DEAR HEALTHCARE PROVIDER LETTER

[date]

IMPORTANT SAFETY INFORMATION Regarding ACTEMRA® (tocilizumab)

Dear Healthcare Provider:

The purpose of this letter is to inform you of important safety information for ACTEMRA® (tocilizumab), an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, and SJIA have not yet been established.

ACTEMRA targets IL-6. FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ACTEMRA to ensure that the benefits of the drug outweigh the potential risks of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies.

You are advised to discuss the risks that may be associated with ACTEMRA therapy with patients and their caregivers.

The ACTEMRA Medication Guide must be provided to patients being treated with ACTEMRA or to their caregiver at the time of first dose or if the Medication Guide is materially changed. This Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy.

IMPORTANT SAFETY INFORMATION ON KNOWN AND POTENTIAL RISKS

Serious Infections

- Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

- ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.
- Prior to initiating ACTEMRA, a test for latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting ACTEMRA. All patients should be monitored for active TB during treatment, even if the initial latent TB test is negative.

Gastrointestinal Perforations

- Events of gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate
- During the six-month Phase 3 RA clinical trials, the overall rate of GI perforations was 0.26 events per 100 patient-years with ACTEMRA therapy versus no events for control.
- ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Potential Risk of 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 clinical studies of adults with RA. Patients should be closely monitored 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.

Potential Risk of Malignancies

- The impact of treatment with ACTEMRA on the development of malignancies is not known, but malignancies were observed in clinical studies. ACTEMRA is an immunosuppressant and treatment with immunosuppressants may result in an increased risk of malignancies.

IMPORTANT INFORMATION ON LABORATORY ABNORMALITIES

Hepatic transaminases, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase 3 clinical trials. Prior to initiating treatment with ACTEMRA, it is recommended that appropriate baseline laboratory parameters be measured. While on ACTEMRA, liver aminotransferases (ALT, AST), neutrophil counts, and platelet counts should be measured every 4 to 8 weeks for RA and PJIA and at the time of the second infusion and, thereafter, every 2 to 4 weeks for SJIA. Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter for RA, PJIA, and SJIA. Dosage modifications may be required if laboratory abnormalities occur. Please see the accompanying full Prescribing Information for more information.

REPORTING ADVERSE EVENTS

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information you provide about these events may inform therapy and monitoring decisions.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

FULL PRESCRIBING INFORMATION AND MEDICATION GUIDE

This letter is not a comprehensive description of the risks associated with the use of ACTEMRA. Please read the accompanying full Prescribing Information that includes the Medication Guide for a complete description of these risks.

This Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy.

Should you require additional copies of the ACTEMRA Medication Guide, you may:

- Request copies from Genentech by calling the toll-free medical information line at 1-800-ACTEMRA (1-800-228-3672)
- Print copies of the Medication Guide from the ACTEMRA Web site at www.ACTEMRA.com

For more information, please call 1-800-ACTEMRA or visit www.ACTEMRA.com

Sincerely,

Hal Barron, MD
Chief Medical Officer, USA
Genentech, Inc.

Enclosure

ATTACHMENT B: PRESCRIBER EDUCATION SLIDE DECK

ACTEMRA Risk Mitigation Strategy

*Presenter Name, Degree
Medical Science Liaison
Genentech, Inc*



Overview of AEs of Special Interest

- Serious Adverse Events
- Infections, serious infections and opportunistic infections
- Cardiovascular events and elevated lipid parameters
- Malignancies
- Demyelinating disorders
- Gastrointestinal perforations
- Changes in liver function tests
- Decreases in peripheral neutrophil counts and decreases in platelet counts
- Anaphylaxis

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ACTEMRA: Black Box Warning

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacteria, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA.
- If a serious infection develops, interrupt ACTEMRA until the infection is controlled.
- Perform tests for latent TB; if positive, start treatment for TB prior to starting ACTEMRA.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

ACTEMRA: Warnings and Precautions

- ACTEMRA should **NOT** be administered 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.
- Patients should be closely monitored 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.
- ACTEMRA should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis.

Lipids: Warnings and Precautions

Rheumatoid Arthritis

- Treatment with ACTEMRA was associated with increases in lipid parameters such as:
 - Total cholesterol
 - Triglycerides
 - LDL cholesterol
 - HDL cholesterol
- **Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.**
- Patients should be managed according to clinical guidelines for the management of hyperlipidemia.
- Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (e.g., simvastatin, lovastatin, atorvastatin, etc.).

ACTEMRA: Warnings and Precautions

- The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies.
- ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

ACTEMRA: Warnings and Precautions

- 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.
- Patients should be closely monitored 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.

ACTEMRA: Warnings and Precautions

- Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients.
- ACTEMRA should be used with caution in patients who may be at increased risk for gastrointestinal perforation.
- Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Liver Enzyme Abnormalities: Monitoring and Dosage Modifications

- It is recommended that ACTEMRA **NOT** be initiated in patients who have ALT or AST above 1.5 times the upper limit of normal (ULN).
- ALT and AST levels should be monitored every 4 to 8 weeks. When clinically indicated, other liver function tests such as bilirubin should be considered.

Elevated Liver Enzyme

ALT or AST values	Recommendation
> 1 to 3 x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg per kg or interrupt ACTEMRA until ALT or AST have normalized
> 3 to 5 x ULN (confirmed by repeat testing)	Interrupt 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
> 5 x ULN	Discontinue ACTEMRA

Neutrophils: Monitoring and Dosage Modifications

- It is recommended that ACTEMRA **NOT** be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm³.
- Neutrophils should be monitored every 4 to 8 weeks.

Neutropenia Risk Mitigation

ANC (cells/mm ³)	Recommendation
> 1000	Maintain Dose
500 – 1000	Interrupt ACTEMRA dosing When ANC greater than 1000 cells per mm ³ resume TCZ at 4 mg per kg and increase to 8 mg per kg as clinically appropriate
< 500	Discontinue ACTEMRA

Platelets: Monitoring and Dosage Modifications

- It is recommended that ACTEMRA **NOT** be initiated in patients with a platelet count $< 100,000/\text{mm}^3$.
- Platelets should be monitored every 4 to 8 weeks.

Thrombocytopenia Risk Mitigation

Platelet count (cells/mm ³)	Recommendation
50,000 – 100,000	Interrupt ACTEMRA dosing When platelet count is greater than 100,000 cells per mm ³ resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate
$< 50,000$	Discontinue ACTEMRA

ACTEMRA: Warnings and Precautions

- ACTEMRA should **NOT** be administered to patients with known hypersensitivity to ACTEMRA.
- Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with 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, and in 0.2% (8 out of 4009) of patients in the all-exposure rheumatoid arthritis population.
- ACTEMRA should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis.
- If anaphylaxis or other clinically significant hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately and ACTEMRA should be permanently discontinued.



**ATTACHMENT C: JOURNAL INFORMATION PIECE FOR
EMERGENCY MEDICINE PHYSICIANS AND EMERGENCY
MEDICAL SERVICES PROFESSIONALS**

**Important Safety Information for Emergency Medicine Physicians
About Potential Risks of Infection and Gastrointestinal
Perforation With ACTEMRA®**

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, and SJIA have not yet been established.

Emergency medicine physicians should be aware of important safety information regarding ACTEMRA®.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death. These infections include tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Gastrointestinal perforations: Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis. Reported perforations have involved generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

In addition to these adverse events, patients treated with ACTEMRA may have elevated hepatic transaminases (ALT, AST) and lipids, and decreased neutrophils and platelet counts. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

Reporting Adverse Events

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

**ATTACHMENT D: JOURNAL INFORMATION PIECE FOR
GASTROENTEROLOGISTS AND HEPATOLOGISTS**

Important Safety Information for Gastroenterologists and Hepatologists About Potential Risks of Gastrointestinal Perforation and Transaminase Elevations With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, and SJIA have not yet been established.

Gastroenterologists and **hepatologists** should be aware of important safety information regarding ACTEMRA.

Gastrointestinal perforations: Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Transaminase elevations: Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations (ALT, AST) in Phase 3 clinical trials. These elevations did not result in apparent permanent or clinically evident hepatic injury with modification of the treatment regimen, which resulted in a decrease or normalization of liver enzymes. Patients receiving ACTEMRA should be monitored for elevated transaminase levels and dose modifications may be necessary. When clinically indicated, other liver function tests, such as bilirubin, should be considered. Please see the full Prescribing Information for more information.

Reporting Adverse Events

It is important that you report any serious gastrointestinal adverse events, including GI perforation, hepatic disease or hepatic impairment, that occur in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a gastroenterologist or hepatologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

**ATTACHMENT E: JOURNAL INFORMATION PIECE FOR
INFECTIOUS DISEASE SPECIALISTS**

Important Safety Information for Infectious Disease Specialists About Potential Risks of Infections With ACTEMRA[®]

ACTEMRA[®] (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA[®] dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA[®] dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA[®] dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA[®] for conditions other than RA, PJIA, and SJIA have not yet been established.

Infectious disease specialists should be aware of important safety information regarding ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.

Reporting Adverse Events

It is important that you report all serious infections that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as an infectious disease specialist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

**ATTACHMENT F: JOURNAL INFORMATION PIECE FOR
INTERNISTS AND INTERNAL MEDICINE SUBSPECIALISTS**

Important Safety Information for Physicians About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, and SJIA have not yet been established.

Physicians should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Gastrointestinal perforations: Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

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 clinical studies of adults with RA. Patients should be closely monitored 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.

Malignancies: Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Laboratory abnormalities: Hepatic transaminases (ALT, AST), lipids, neutrophils, and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase 3 clinical trials. Dosage modifications may be

required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

Reporting Adverse Events

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing internist and/or internal medicine subspecialist, such as a rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

**ATTACHMENT G: JOURNAL INFORMATION PIECE FOR
NEUROLOGISTS**

Important Safety Information for Neurologists About Demyelinating Disorders in Co-managing Rheumatoid Arthritis Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, and SJIA have not yet been established.

Neurologists co-managing RA patients should be aware of important safety information regarding treatment with ACTEMRA.

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 clinical studies of adults with RA. Patients should be closely monitored 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.

Reporting Adverse Events

It is important that you report any serious neurologic adverse event, including demyelinating disorders, that occurs in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a neurologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

**ATTACHMENT H: JOURNAL INFORMATION PIECE FOR
ONCOLOGISTS**

Important Safety Information for Oncologists About Malignancy Risk With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, and SJIA have not yet been established.

Oncologists should be aware of important safety information about ACTEMRA.

Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Reporting Adverse Events

If you are consulted to see a patient with cancer at any time after receiving ACTEMRA therapy, it is important that you report the case, even if you do not think there is a causal relationship. The information that you, as an oncologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

**ATTACHMENT I: JOURNAL INFORMATION PIECE FOR
RHEUMATOLOGISTS**

Important Safety Information for Rheumatologists About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, and SJIA have not yet been established.

Rheumatologists should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Gastrointestinal perforations: Gastrointestinal (GI) perforation have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

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 clinical studies of adults with RA. Patients should be closely monitored 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.

Malignancies: Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Laboratory abnormalities: Hepatic transaminases (ALT, AST), lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated

with ACTEMRA treatment in Phase 3 clinical trials. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

Reporting Adverse Events

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for full Prescribing Information and Medication Guide.

ATTACHMENT J: ACTEMRA REMS WEBSITE SCREENSHOT



Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits outweigh its risks.

To learn more about serious risks, read the [Important Safety Information](#) and [Medication Guide](#) and discuss it with your patients.

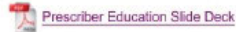
The goal of the ACTEMRA REMS is:

- To inform healthcare providers about the serious risks associated with ACTEMRA.

Genentech recommends laboratory monitoring of patients being treated with ACTEMRA due to the potential consequences of treatment-related abnormalities in liver function, lipids, neutrophils and platelets. If you become aware of a patient who has developed a serious adverse event while being treated with ACTEMRA, it is important that you report the case, even if you do not think there is a causal relationship. The information you provide about these events may inform therapy and monitoring decisions.

Continue to check back on this Web site, it will be updated to include additional information intended to assist in the proper communication of the risks and benefits of ACTEMRA.

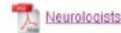
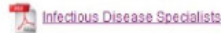
Prescriber Education Slide Deck



Healthcare Professional Letter



Journal Information Pieces



For more information on safety, please [click here](#).

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

/s/

SALLY M SEYMOUR
04/29/2013
for Badrul Chowdhury

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: April 29, 2013

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review
BLA Number: 125-276, supplement 64
Applicant Name: Hoffman-LaRoche
Date of Submission: June 28, 2012
PDUFA Goal Date: April 29, 2013
Proprietary Name: Actemra
Established Name: Tocilizumab
Dosage form: Single-use vials for intravenous infusion
Strength: 20 mg/mL single-use vial
Proposed Indications: Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older either given alone or in combination with methotrexate

Action: Approval

1. Introduction

Hoffman-La Roche submitted a BLA supplement seeking approval for Actemra either given alone or in combination with methotrexate for the treatment of active polyarticular idiopathic arthritis (pJIA) in patients 2 years of age and older. Actemra is currently approved for treatment of Rheumatoid Arthritis (RA) and systemic juvenile idiopathic arthritis (sJIA). The proposed dose of Actemra for pJIA is 10 mg/kg every 4 weeks for patients weighing less than 30 kg and 8 mg/kg every four weeks for patients weighing 30 kg or higher. The application is primarily based on one clinical efficacy and safety study. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety study.

2. Background

Polyarticular juvenile idiopathic arthritis (pJIA) is a category of juvenile idiopathic arthritis (JIA) that affects approximately 2 to 17% of children with JIA (prevalence of JIA has been estimated to be between 57 and 220 per 100,000 children younger than 16 years of age). pJIA is similar to adult RA with articular manifestations being predominant. There are three biologic products currently FDA approved for the treatment of pJIA, two TNF-inhibitors, adalimumab (Humira) and etanercept (Enbrel), and one targeting T-cell co-stimulatory signaling pathway, abatacept (Orencia). Of the small molecule agents, various NSAIDs, corticosteroids, sulfasalazine, and methotrexate are FDA approved for Juvenile Rheumatoid Arthritis (JRA), which is an old terminology that encompasses pJIA.

The primary data submitted by Hoffman-La Roche to support this application is from one controlled clinical trial (Study WA 19977) that was also a PREA-required study from adult RA approval. Study WA 19977 was conducted under a special protocol agreement.

3. Chemistry, Manufacturing, and Controls

Actemra is an approved marketed product and there are no CMC issues. No new data were submitted with this supplement for review.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required for this application. With the sJIA application, Hoffman-La Roche previously submitted a juvenile toxicity and reproductive development study in mice using a murine surrogate antibody. There were no treatment related effects on the maturity and development of mice after treatment with the murine surrogate antibody. These study results are included in the pediatric section of the label.

5. Clinical Pharmacology and Biopharmaceutics

No dedicated clinical pharmacology studies were required or performed for this application. PK data in pJIA patients came from population PK reports based on PK samples collected from the pivotal trial WA 19977 and other supportive clinical studies. Results from these analyses were included in the PK section of the label. The rest of the clinical pharmacology data applicable for the pJIA program was obtained in the adult program for RA and pediatric program for sJIA, which were previously reviewed.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

This submission is based on one study (Study WA 19977) as mentioned in Section 2 above, and additional supportive Japanese studies MRA 318 and MRA 319. A limited program was acceptable because the number of patients with pJIA is small, and Actemra is already approved for RA and sJIA.

b. Design and conduct of the study

WA 19977 was a multicenter, multinational (58 centers in 15 countries, 13% patients were from North America), randomized, double-blind, placebo-controlled, parallel group study conducted in patients 2-17 years of age with active pJIA. Eligible patients (n=188) were initially treated for 16 weeks with open-label Actemra infusion every 4 weeks at a dose of 8 or 10 mg/kg for patients weighing less than 30 kg and 8 mg/kg for patients weighing 30 kg or higher (Part I of the study, completed). Patients achieving at least 30% improvement (JIA ACR30 response) at week 16 (n=163, ITT) entered in a 24-week

double-blind, placebo-controlled, randomized withdrawal period in a 1:1 ratio to treatment with Actemra or placebo (Part II of the study, completed). Patients who completed Part II (n=158) then entered in 64-week open-label extension (Part III of the study, ongoing). The primary efficacy endpoint of the study was the proportion of patients who developed a JIA ACR 30 flare by week 40 (i.e., during Part II of the study) relative to week 16 (i.e., at end of Part I of the study). JIA ACR 30 flare was defined as three of six core JIA outcome variables worsening by at least 30%, with no more than one of the remaining variables improving by more than 30%, and a minimum worsening of two active joints and at least 20 units worsening in the global assessment (on a scale of 0 to 100).

c. Efficacy findings and conclusions

The submitted clinical program supports use of Actemra either given alone or in combination with methotrexate for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older. Results for the primary efficacy endpoint are shown in Table 1. Other secondary measures of efficacy were also supportive (data not shown in this document).

Table 1. Proportion of patients with JIA ACR30 flare by week 40 relative to week 16 (ITT)

	Placebo N=81	Actemra N=82
Flared, n (%)	39 (48%)	21 (26%)
95% CI	0.37, 0.59	0.16, 0.35
Weighted difference vs. placebo	-	-0.21
P-value	-	0.0024

8. Safety

a. Safety database

The safety profile of Actemra in patients with rheumatoid arthritis has already been established. The safety data with Actemra in patients with pJIA comes from the single study WA 19977 described above in section 7. Given the limited population and the known safety information from other populations, the safety database in patients with pJIA is acceptable for approval. However, long term safety of use of Actemra in pJIA patients is unknown and a post-marketing safety study will be required to evaluate risks such as malignancies, serious infections, gastrointestinal perforations, and effect on skeletal growth and development. Actemra will be the first IL-6 targeting product for pJIA. IL-6 has known effects on immune and skeletal system development, and existing safety data for Actemra in pediatric patients are limited.

b. Safety findings and conclusion

The safety review of the WA 19977 study did not identify a new safety signal for Actemra.

c. REMS/RiskMAP

Actemra was originally approved for RA with a REMS that included a medication guide and communication plan. The Medication Guide is no longer part of the REMS consistent with the Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) No new safety signals were identified during review of this pJIA application. However, the REMS was modified to update the new indication but otherwise will remain essentially unchanged.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Actemra is an approved product with known safety profile and the safety profile in this patient population did not reveal a new safety signal. The single clinical study had typical design of an arthritis indication and the efficacy findings were quite robust. There were no new or unique safety findings seen. Thus, this application did not raise any issues that warranted discussion at an advisory committee meeting.

10. Pediatric

Study WA 19977 was conducted as a PREA requirement for the original RA approval for Actemra. The applicant received an orphan designation for the pJIA indication on July 31, 2012, thus new PREA requirements are not triggered by this new indication. This application was discussed at the Pediatric Review Committee (PeRC) meeting held on February 6, 2013, and the PREA requirement has now been fulfilled. There are no outstanding pediatric issues related to this pJIA application.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was not conducted for this application because there were no study center enrolling a large number of patients and the efficacy findings were consistent across centers. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name as the name Actemra was previously reviewed and found to be acceptable. The product is currently marketed under the trade name Actemra.

b. Physician Labeling

The labeling of Actemra was reviewed previously with the original approval of the product and a subsequent supplement. With these applications the existing label will be updated to include the new information regarding the claim of treating patients with pJIA. The main changes are in the Clinical Studies section where new data from the study WA 19977 are described. In addition there will be some changes in other relevant sections of the label.

c. Carton and Immediate Container Labels

Actemra is a marketed product and there were no changes to the carton and immediate container labels with this application.

d. Patient Labeling and Medication Guide

There are no data that warrant major changes to the currently approved patient labeling and Medication Guide. Minor changes reflecting the new study supporting use of Actemra in patients with pJIA will be included.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval for Actemra either given alone or in combination with methotrexate for the treatment of active pJIA in patients 2 years of age and older. The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of Actemra either given alone or in combination with methotrexate for the treatment of active pJIA. The efficacy finding was robust. Actemra has safety concerns, including serious infections, gastrointestinal perforation, and changes in blood counts and liver function tests. The clinical program submitted to support this new indication was limited in size due to the patient population, but no unique safety signal was identified.

c. Post-marketing Risk Management Activities

Actemra has REMS with required periodic assessments, and a communication plan. These remain unchanged as no new safety signals were identified in review of this submission.

d. Post-marketing Study Commitments

Hoffman-La Roche will conduct a long-term safety study in 800 pediatric patients 2-17 years of age with pJIA treated with Actemra or other biologics (400 patients per arm) to

evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of pediatric pJIA patients. Patients will be followed for 5 years. The long-term safety study was required because unlike sJIA, where no long-term safety data was required, there are other treatment options available for pJIA. Actemra will be the first IL-6 targeting product for pJIA. IL-6 has known effects on immune and skeletal system development, and existing safety data for Actemra in pediatric patients are limited.

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/s/

SALLY M SEYMOUR
04/29/2013
for Dr. Badrul Chowdhury

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: sBLA 125276/64

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

1. Bowen, Philantha
2. Buenconsejo, Joan
3. Chowdhury, Badrul
4. Doddapaneni, Suresh
5. Falter, Matthew
6. Feldman, Gerald
7. Hulett, Melissa
8. Jafari, Ladan
9. Kim, Yongman
10. Merchant, Lubna
11. Nikolov, Nikolay
12. Rains, Kimberly
13. Robison, Timothy
14. Seymour, Sally
15. Shapiro, Marjorie
16. Szydlo, Roberta
17. Williams, Sharon
18. Yancey, Carolyn
19. Yim, Sarah

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 8, 2013
From	Sarah (Okada) Yim, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	sBLA 125276/64
Supplement#	
Applicant	Hoffman La Roche, Inc.
Date of Submission	Received June 29, 2012
PDUFA Goal Date	April 29, 2013
Proprietary Name / Established (USAN) names	Actemra (tocilizumab)
Dosage forms / Strength	Single use vials of 20 mg/mL: 80 mg/4mL, 200 mg/10mL, 400 mg/20 mL, for IV infusion (No new dosage forms or strengths were proposed)
Proposed Indication(s)	Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis
Recommended:	<i>Approval, with revisions to proposed label</i>

1. Introduction

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). Tocilizumab selectively binds to soluble and membrane-bound human IL-6R, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6. IL-6 is a pleiotropic cytokine that has important roles in the regulation of the immune response, inflammation, and hematopoiesis. IL-6 is the primary driver of acute phase reactants, and hepatocytes express high levels of IL-6R. Elevated tissue and serum levels of IL-6 have been implicated in the pathophysiology of RA.

The original biologic license application (BLA) for tocilizumab in rheumatoid arthritis (RA) was submitted November 19, 2007, and received a complete response on September 17, 2008, due to deficiencies in the nonclinical program and on inspection of the manufacturing facilities. These deficiencies were addressed in a complete response submission which was submitted July 9, 2009 and approved on January 8, 2010. TCZ is the first IL-6 inhibitor approved for use in the United States. TCZ was approved in the U.S. for Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years of age and older on April 15, 2011.

Roche's co-development partner, Chugai Pharmaceutical Co. Ltd., received approval in Japan in April 2005 for the use of TCZ in the treatment of multi-centric Castleman's Disease, a rare B-cell lymphoproliferative disorder. In April 2008, TCZ was approved in Japan for the treatment of adult RA, systemic juvenile idiopathic arthritis (SJIA), and polyarticular juvenile idiopathic arthritis (PJIA). Other than Japan, TCZ has been approved for PJIA in India. TCZ

has been approved for the treatment of moderately to severely active RA patients in the European Union (27 countries) and ~80 other countries worldwide. In addition to Japan and the US, TCZ has been approved for SJIA in the 27 EU countries, India, Mexico, Canada, Switzerland, and Ukraine.

The present supplemental BLA is for a new indication in patients with Polyarticular Juvenile Idiopathic Arthritis (PJIA) 2 years of age and older. The primary data in support of this application are derived from a single study (WA19977) which is also a PREA-required study (from the adult RA approval) and which was conducted under a Special Protocol Assessment (SPA) agreement.

2. Background

The classification system historically used to characterize arthritis in children and adolescents used the nomenclature of Juvenile Rheumatoid Arthritis (JRA), as defined by the American College of Rheumatology (ACR). This classification system distinguished categories of disease into pauciarticular, polyarticular and systemic disease.

However, pediatric rheumatologists favored the more detailed classification system proposed by the International League of Associations for Rheumatology (ILAR), and this is the classification system now used by the rheumatology academic community. Table 1 below summarizes the ILAR classification system. Juvenile Idiopathic Arthritis is the umbrella term used to encompass all the subtypes listed. Broadly, JIA is defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses (such as infections, malignancy, trauma, reactive arthritis, and specific connective tissue diseases such as systemic lupus erythematosus) have been excluded. JIA affects an estimated 294,000 children between the ages of 0 and 17 in the United States.¹ The incidence, prevalence and disease characteristics of JIA vary worldwide, reflecting genetic and environmental factors that influence the disease phenotype.

SJIA, for which TCZ is already approved, is characterized by marked systemic inflammation and extra-articular involvement. PJIA, the subject of this application, is most similar to adult RA, with articular manifestations being predominant.

In addition to corticosteroids, sulfasalazine and methotrexate, three biologic disease-modifying anti-rheumatic drugs (DMARDs) have been approved for PJIA: etanercept (Enbrel®), approved for patients 2 years of age and older; adalimumab (Humira®), approved for patients 4 years of age and older; and abatacept (Orencia®), approved for patients 6 years of age and older. If approved, TCZ would be the first in the class of IL-6 inhibitors to be approved for the treatment of PJIA.

¹ M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," *Pediatrics in Review*, 2012; 33:303-313

Table 1: International League of Associations for Rheumatology (ILAR) Juvenile Idiopathic Arthritis (JIA) Classification²

Category	Definition	Frequency (% of all JIA)	Age of Onset	Sex Ratio	Susceptibility Alleles
Systemic onset juvenile idiopathic arthritis (JIA)	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented as daily ("quotidian") for at least 3 days and accompanied by one or more of the following: (1) rash (evanescent), (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, (4) serositis	4%–17%	Childhood	F=M	HLA-DRB1*11
Oligo JIA	Arthritis affecting one to four joints during the first 6 months of disease	27%–56%	Early childhood; peak at 2–4 years	F>>>M	HLA-DRB1*08 HLA-DRB1*11 HLA-DQA1*04 HLA-DQA1*05 HLA-DQB1*04 HLA-A2 (early onset)
• Persistent	Affects no more than four joints throughout the disease course				
• Extended	Affects more than four joints after the first 6 months of disease				
Polyarthritis (RF-negative)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are negative	11%–28%	Biphasic distribution; early peak at 2–4 years and later peak at 6–12 years	F>>>M	HLA-DRB1*0801
Polyarthritis (RF-positive)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are positive on at least two occasions that are 3 months apart	2%–7%	Late childhood or adolescence	F>>>M	HLAB1*04 HLA-DR4
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least two of the following: (1) dactylitis, (2) nail pitting, (3) family history of psoriasis in a first-degree relative	2%–11%	Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years	F>M	HLA-B27 IL23R ¹ (new association)
Enthesitis-related arthritis	Arthritis or enthesitis with at least two of the following: (1) sacroiliac tenderness or lumbosacral pain, (2) presence of HLA-B27 antigen, (3) onset of arthritis in a male >6 years old, (4) acute anterior uveitis, (5) family history in a first-degree relative of HLA-B27-associated disease	3%–11%	Late childhood or adolescence	M>>>F	HLA-B27 ERAP1 ¹ (new association)
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in two or more of the above categories	11%–21%			

Adapted from Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369:767–768.
¹Hinks A, Martin P, Flynn E, et al. Subtype specific genetic associations for JIA: ERAP1 with the enthesitis related arthritis subtype and IL23R with juvenile psoriatic arthritis. *Arthritis Res Ther*. 2011;13:R12. HLA=human lymphocyte antigen; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor.

3. CMC/Device

Primary Product Quality Reviewer: Gerald Feldman, Ph.D.

Product Quality Team Leader: Marjorie Shapiro, Ph.D.

Office of Compliance, Division of Manufacturing and Product Quality (DMPQ) Team Leader: Patricia Hughes

Actemra is approved as liquid-in-vial for intravenous infusion, and this presentation was used for Study WA19977. There were no CMC data submitted for this supplement. However, an updated immunogenicity assay was used in the study and the applicant was requested to describe any differences between this assay and the one used for the original BLA (RA indication). The applicant provided the requested validation data and study reports for the immunogenicity assay used in Study WA19977 along with a comparison to the original BLA assay. Although there were minor quantitative differences between the assays, Dr. Feldman concluded that any differences between the assays would not change the overall results or interpretation of results.

² Espinosa M and BS Gottlieb, "Juvenile Idiopathic Arthritis." *Pediatrics in Review*, 2012; 33:303-313

4. Nonclinical Pharmacology/Toxicology

Juvenile animal studies were submitted with the SJIA application. No additional studies were submitted with this application. A brief summary of the results are as follows:

A segment 3 reproductive safety study using a murine surrogate was submitted with the original BLA and did not show any adverse effects. Results of Study MR16-1: “A Toxicity Study to Evaluate the Effects of MR16-1 on Postnatal Development and Growth in Juvenile Mice,” were submitted with the SJIA application. MR16-1 is a rat IgG surrogate antibody to tocilizumab. This study included a determination of T-cell subtypes and functional assessment of the immune system, along with an assessment of effects on skeletal growth and sexual maturity. Mice were given MR16-1 intravenously every 3 days from day 22 (weaning) until day 79 (maturation) at 0, 15, and 50 mg/kg (single loading dose of 50 mg/kg for the 15 mg/kg dose group). Treated animals were sacrificed on day 79. Animals in the satellite groups were sacrificed on post-natal day 126. Animals were observed for growth, sexual maturation, immuno-phenotyping, antibody response to KLH antigen. Histopathology of protocol specified tissues were conducted at terminal sacrifice in the main group and recovery groups. Data did not show any treatment related effect in juvenile animals with respect to growth, development sexual maturation and immune function up to 50 mg/kg/IV dose. The No-Observed-Effect Level (NOEL) was 50 mg/kg/IV. The pharmacology/toxicology team has previously concluded that these data have not raised any concerns that would preclude approval of tocilizumab for pediatric indications.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Primary Reviewer: Liang Zhao, Ph.D.

Clinical Pharmacology Supervisor: Suresh Doddapaneni, Ph.D.

Pharmacometrics Reviewer: Atul Bhattaram, Ph.D.

The following is excerpted and adapted from Dr. Zhao's and Dr. Nikolov's reviews.

The clinical pharmacology program in support of the PJIA indication included PK and PD data and PK-PD relationships from Roche's pivotal study WA19977 and supportive Chugai studies MRA318JP and MRA319JP. Summary statistics for the PK parameters were calculated from the serum TCZ concentrations derived from Study WA19977 and inputted in the population PK model.

- For doses of 8 mg/kg TCZ (patients weighing ≥ 30 kg) given every 4 weeks, the predicted mean (\pm SD) AUC_{wk12-16}, C_{max} and C_{min} of TCZ were 1231 ± 361 mcg•day/mL, 182 ± 37 mcg/mL and 7.49 ± 8.2 mcg/mL, respectively.
- For doses of 10 mg/kg tocilizumab (patients weighing < 30 kg) given every 4 weeks, the predicted mean (\pm SD) AUC_{wk12-16}, C_{max} and C_{min} of TCZ were 968 ± 254 mcg•day/mL, 175 ± 32 mcg/mL and 2.35 ± 3.59 mcg/mL, respectively.

- The estimated accumulation ratios were 1.05 and 1.16 for AUC4weeks, 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.
- Because of the dependence of total clearance on TCZ serum concentrations, the half life of tocilizumab is also concentration dependent and cannot be reported with a universal value.

Body size as measured by BSA was found to be the most influential covariate for the linear part of and the overall clearance, central volume of distribution, and peripheral volume of distribution. The proposed dose is based on another measure of body size, the body weight, which should be highly correlated to BSA. Therefore, the body weight based dosing strategy by matching PK exposure for different body weight groups is reasonable. The applicant selected the dose regimen of TCZ based on modeling and PK data from MRA318JP, which employed the single dosing regimen of 8 mg/kg every 4 weeks to all 19 enrolled patients. These data showed numerically higher response rates among older patients with higher body weight and higher body mass index, associated with a trend toward lower systemic exposure in patients with lower body weight—particularly 33 kg or less. Modeling and simulation results indicated that to achieve comparable exposure across the range of body weights, TCZ should be dosed at 8 mg/kg for patients with body weight ≥ 30 kg and 10 mg/kg for patients with body weight < 30 kg. Thus Study WA19977 was designed to further assess the relative efficacy and safety of the 8 mg/kg vs. 10 mg/kg dose regimens in patients weighing less than 30 kg.

Immunogenicity

The impact of immunogenicity on PK exposure, efficacy, and/or safety remains inconclusive for the PJIA population, given its low incidence (n=1 in Study WA19977) and the relatively small database.

Conclusion

The clinical pharmacology/biopharmaceutics team concluded that the information submitted was adequate to support approval of the sBLA from their perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Nikolay Nikolov, M.D.
Primary Statistical Reviewer: Yongman Kim, Ph.D.
Statistical Team Leader: Joan Buenconsejo, Ph.D.

Overview of Study Design

Study WA19977 is a pivotal Phase III, randomized, double-blind, placebo-controlled, parallel group, multi-center, withdrawal study conducted in three parts in pediatric patients ages 2 to 17 years with active PJIA. This is an ongoing, international, multicenter trial consisting of three parts:

- Part I: a 16-week open-label run-in period where all patients received TCZ. Patients weighing 30 kg or more received 8 mg/kg TCZ IV every 4 weeks. Patients weighing less than 30 kg were randomized to receive either 8 or 10 mg/kg.
- Part II: a 24-week double-blind, placebo-controlled, randomized withdrawal period in patients achieving a JIA ACR30 response at Week 16 of part I. Patients received the same dose of TCZ as in Part I or received placebo. Patients experiencing a flare or completing Part II then proceeded to Part III.
- Part III: a 64-week ongoing open-label extension.

The WA19977 study protocol and statistical analysis plan was the subject of three regulatory interactions with the sponsor, finally culminating in a SPA agreement.

MRA318JP is a 12-week open-label single-arm study where 19 Japanese patients between the ages of 3 to 19 years received TCZ 8 mg/kg IV every 4 weeks. MRA319JP is the long-term extension of MRA318JP; patients continued treatment for up to 3.5 years.

Study Population

Study WA19977 enrolled a total of 188 patients at 58 centers in 15 countries worldwide, including the US (7 centers). Twenty-four patients (13%) were from North America. Sixty three percent (119/188) of patients weighed ≥ 30 kg upon study entry and received TCZ 8 mg/kg every 4 weeks. Sixty nine patients weighed < 30 kg upon study entry and were randomized to receive TCZ 8 mg/kg every 4 weeks (n = 34) or TCZ 10 mg/kg every 4 weeks (n = 35). The baseline demographic and disease characteristics of the patients were otherwise roughly similar in each treatment group. Consistent with the underlying disease, study patients were most likely to be female (over 70% of each group) and Caucasian (approximately 80% of each group). Over 75% of each group were receiving methotrexate at the time of study entry, and 40-50% were receiving corticosteroids. Patients in each group had a similar level of disease activity (~20 active joints, average ESR ~35).

Table 2: Patient Disposition, Part I (Week 16), Study WA19977

	BW <30 kg		BW ≥ 30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Randomized and treated	35	34	119	188
Completed Part I, n (%)	31 (89)	24 (71)	111 (93)	166 (88)
Discontinuations, n (%)	4 (11)	10 (29)	8 (7)	22 (12)
<i>Lack of efficacy (JIA ACR30 response)</i>	4 (11)	6 (18)	5 (4)	15 (8)
<i>Adverse events</i>	0	1	2	3
<i>Withdrew consent</i>	0	2	1	3
<i>Lost to follow up</i>	0	1	0	1

Source: CSR WA19977, adapted from Figure 1 and Tables stex11_1, slae01_wd_ae; Table 7 of Dr. Nikolov's review.
 BW-body weight

As summarized above in Table 2, of the 188 patients randomized and treated in Part I of the study, 166 patients completed. A relatively higher proportion of patients discontinued from the study in the TCZ 8 mg/kg group of the <30 kg body weight category, primarily due to lack of efficacy. This is consistent with the efficacy results from the study, which will be discussed in further detail below. Table 3 below summarizes patient disposition in the withdrawal portion of the study. Of the 166 patients who were randomized in Part II, all but 5 patients completed. Of the patients randomized in Part II, 11/81 (13%) placebo patients and 9/82 (10%) TCZ patients were from North America.

Table 3: Patient Disposition, Part II (Week 40) in Study WA19977

	TCZ (N=82)			Placebo (N=84)		
	BW <30 kg		BW ≥30 kg	BW <30 kg		BW ≥30 kg
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg
Randomized and treated, ITT	16	11	55	15	13	53**
Completed Part II, n (%)	15 (94)	11 (100)	52 (95)	15 (100)	13 (100)	52 (98)
Discontinuations	1	0	3	0	0	1
<i>Adverse events</i>	1	0	0	0	0	1
<i>Withdrew consent</i>	0	0	3*	0	0	0

Source: CSR WA19977, adapted from Figure 2 and Table stex11_2, slae01_wd_ae; Table 8 of Dr. Nikolov's review
 BW-body weight
 * Patient 2583 missed the Week 16 infusion, completed Week 18 and then withdrew at the next visit; Patients 2122 and 2682 withdrew while receiving Part II escape medication.
 ** A total of 56 patients were randomized but three patients received no infusion in Part II and were not included in the ITT population (table stec11_rnd a 2)

Efficacy Results

Analogous to the ACR Response Criteria for adults, the ACR created a composite response endpoint for children with JIA which has become the standard primary endpoint for use in JIA clinical trials. The core variables for this endpoint include:

- Parent/patient global assessment of overall well-being
- Physician global assessment of disease activity
- Number of joints with active arthritis
- Number of joints with limitation of movement
- Child Health Assessment Questionnaire (CHAQ)
- Erythrocyte sedimentation rate (ESR)

A response is defined as a certain minimum level of improvement, typically 30%, in at least 3 of the 6 core variables, with no more than 30% worsening in 1 of the remaining variables. In Study WA19977, the level of response after starting treatment was only descriptively assessed in Part I, which was not controlled. The primary efficacy outcome was the proportion of patients developing a JIA ACR 30 flare relative to Week 16 during Part II of the study (the

randomized withdrawal phase from Week 16 to Week 40). JIA ACR 30 flare was defined as worsening in 3 of 6 core variables by at least 30%, with no more than 30% improvement in one of the remaining variables AND a minimum worsening of two active joints and an at least 20 unit worsening in the global assessments (on a scale of 0 to 100).

Primary Endpoint

Results for the primary endpoint are summarized in Table 4, below. A significantly higher proportion of patients randomized to placebo experienced a flare during Part II of the study.

Table 4: Primary Endpoint: Proportion with JIA ACR30 Flare by Week 40 Relative to Week 16 (ITT)

N	All Placebo 81	All TCZ 82
Flared, n (%)	39 (48%)	21 (26%)
95% CI	0.37, 0.59	0.16, 0.35
Weighted difference vs. PBO	-	-0.21
p-value		0.0024

Source: CSR WA19977, adapted from Table etepcmh03_ja3fv_v1_rx2_it2_p2; Table 10 from Dr. Nikolov's review

Keeping in mind the relatively small number of patients experiencing flare during the randomized withdrawal period subgroup analyses of the primary endpoint were conducted by gender, race, age, and geographic region. Overall, subgroup analyses were consistent with the primary endpoint results. However in the small non-Caucasian subgroup, 6/17 (35%) of patients experienced a flare in both the placebo and TCZ treatment groups. In Dr. Yongman Kim's analysis by geographic region, he broke the group into EU vs. non-EU regions since this resulted in a somewhat even subgrouping. In this analysis, there was a smaller difference vs. placebo in the non-EU regions, but the trend was consistent with the overall results. Because so relatively few patients were from the US, no subgroup analysis on the basis of US vs. non-US region could be done. Subgroup analyses by background MTX and background corticosteroid use did not suggest an interaction between either of these characteristics and overall treatment effect on flare.

Secondary Endpoints

The applicant used a hierarchical fixed-sequence approach to control for Type I error in the analysis of 12 secondary endpoints pre-specified to be assessed at Week 40, the end of Part II of the study. Results for these secondary endpoints are summarized in Table 5 below. A benefit in favor of TCZ treatment is consistently observed for all endpoints, although the change from baseline in number of joints with limitation of movement was not significantly different between groups. Thus p-values were not provided for any endpoints falling below this endpoint in the sequence. The endpoints selected included multiple levels of improvement from baseline in the JIA ACR Response criteria, changes from baseline in the individual core variables of the response criteria, change from baseline in the CHAQ, and proportion of patients achieving "inactive disease" (as defined by the sponsor and not a widely accepted definition).

Table 5: Overview of the Hierarchical Analysis of Significance Testing for the Secondary Endpoints at Week 40, Applicant’s Analysis

	Endpoint	All Placebo N=81	All TCZ N=82	p-value
Secondary Endpoints				
2	Proportion of patients with JIA ACR30 Improvement Number (%)	44 (54.3%)	61 (74.4%)	0.0084
3	Proportion of patients with JIA ACR50 Improvement Number (%)	42 (51.9%)	60 (73.2%)	0.0050
4	Proportion of patients with JIA ACR70 Improvement Number (%)	34 (42.0%)	53 (64.6%)	0.0032
5	Change from baseline in number of active joints Adjusted Mean	- 11.4	- 14.3	0.0435
6	Change from baseline in Physician’s global assessments VAS Adjusted Mean	- 35.2	- 45.2	0.0031
7	Change from Baseline in the Pain VAS Adjusted Mean	- 22.3	- 32.4	0.0076
8	Change from baseline in number of joints with limitation of movement, Adjusted Mean	- 7.7	- 9.5	0.1229
9	Patient/parent global assessment VAS Adjusted Mean	- 24.7	- 32.1	*****
10	Change from baseline in ESR (mm/hr) Adjusted Mean	- 12.0	- 26.3	*****
11	CHAQ-DI score	- 0.6	- 0.8	*****
12	Proportion with JIA ACR90 improvement Number (%)	19 (23.5%)	37 (45.1%)	*****
13	Proportion with Inactive Disease Number (%)	12 (14.8%)	26 (31.7%)	*****

***** p-values for these variables are not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity

Sources: etepcmh03_ja3fw_v1_rx2_it2_p2 [page 422](#); etepcmh03_jajr_w40_rx2_it2_ap12 [page 424](#); etefano01l_jcrc_w40a_nr_rx2_it2_ap12 [page 426](#); etefano01l_pnvc_w40a_nr_rx2_it2_ap12 [page 9222](#); etepcmh03_ind_w40_rx2_it2_p12 [page 427](#)
 Source: Table 9 of the WA19977 CSR

Response by dosing regimen

Because only responders are randomized for the withdrawal portion in a randomized withdrawal study, treatment effect size in terms of response is not estimable. Therefore, ACR responses in the first 16 weeks of the study were used to explore relative responses by dose regimen, particularly in the under 30 kg weight group, where patients were randomized to

receive either TCZ 10 mg/kg or TCZ 8 mg/kg. As shown in Table 6 below, results through Week 16 were consistent with the data obtained from MRA318JP—patients in the <30 kg weight group who received the same dose regimen as the ≥30 kg weight group (8 mg/kg) had lower relative responses. Patients <30 kg who received TCZ 10 mg/kg had responses that were similar in magnitude to patients ≥30 kg. Population PK analyses from Study WA19977 also confirmed that the 10 mg/kg dose regimen in children weighing <30 kg provides a better exposure match to the ≥30 kg group receiving the 8 mg/kg regimen. Although these data are not controlled and treatment effect size cannot be definitively determined, the proportion of patients experiencing at least 30% improvement in the JIA ACR Responses with TCZ treatment was high in each group.

Table 6: JIA ACR Response at Week 16, by Dosing Regimen, Study WA19977

	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
N	35	34	119	188
ACR30, n (%)	31 (89%)	26 (77%)	111 (93%)	168 (89%)
ACR50, n (%)	28 (80%)	24 (71%)	104 (87%)	156 (83%)
ACR70, n (%)	22 (63%)	14 (41%)	81 (68%)	117 (62%)
ACR90, n (%)	11 (31%)	8 (24)	30 (25%)	49 (26%)

Source: CSR WA19977, adapted from Tables 10 and etepfrq01_w16_it1_ap1; Table 35 of Dr. Nikolov's review

Response by Methotrexate Use

Table 7: Proportion of Patients Experiencing Selected Levels of Improvement in JIA Responses at Week 16, By Dosing Regimen and Baseline MTX Use

	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg N=35	TCZ 8 mg/kg N=34	TCZ 8 mg/kg N=119	N=188
Baseline MTX Use				
Yes, n	29	30	89	148
JIA ACR30, n (%)	26 (90%)	24 (80%)	85 (96%)	135 (91%)
JIA ACR50, n (%)	23 (79%)	22 (73%)	79 (89%)	124 (84%)
JIA ACR70, n (%)	18 (62%)	13 (43%)	64 (72%)	95 (64%)
JIA ACR90, n (%)	9 (31%)	7 (23%)	29 (33%)	45 (30%)
No, n	6	4	30	40
JIA ACR30, n (%)	5 (83%)	2 (50%)	26 (87%)	33 (83%)
JIA ACR50, n (%)	5 (83%)	2 (50%)	25 (83%)	32 (80%)
JIA ACR70, n (%)	4 (67%)	1 (25%)	17 (57%)	22 (55%)
JIA ACR90, n (%)	2 (33%)	1 (25%)	1 (3%)	4 (10%)

Source: CSR WA19977, adapted from Table etepfrq01_w16_bmtx_it1_ap1; Table 29 of Dr. Nikolov's review

At baseline, approximately 80% of patients were taking methotrexate (MTX), and MTX-use was a pre-specified stratification factor for randomization, so the proportion of MTX users was similar among treatment groups. As summarized in Table 7 above, the proportion of

responders at every improvement level was higher in patients who were receiving concomitant MTX. The additional benefit of MTX is similarly noted when evaluating flare rates during Part II of the study and the proportion of responders at the end of Part II (data not shown—refer to Dr. Nikolov’s review for details). This does not appear to be related to an effect on immunogenicity, as immunogenicity was low (see Section 8).

- **Statistical and Clinical efficacy conclusions**

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

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

No other notable efficacy issues or outstanding efficacy issues were identified.

8. Safety

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

In addition to the safety database from the PJIA and SJIA specific studies, the safety database of tocilizumab in adult RA patients includes 4009 patients with an exposure amounting to almost 15,000 patient-years. There has also been a longer post-marketing history for TCZ in Japan, where it was first approved in 2005 for the treatment of multicentric Castleman’s disease, and for the treatment of RA, PJIA, and SJIA since April 2008. As a requirement of approval in Japan, postmarketing surveillance programs (open-label, non-comparative patient registries) were enacted that were required to capture all post-marketing patients up until August 2010, at which time more typical postmarketing pharmacovigilance was commenced.

Overall, these data remain consistent with safety data previously submitted for tocilizumab, and no new safety signals have been identified. The major risk of TCZ is serious infections, consistent with its potent immunosuppressive effects. TCZ manifested effects on laboratory parameters, such as decreased white blood cell count, increases in lipids, and most significantly, liver enzyme elevation, although these continue to lack significant association with clinical adverse events. TCZ currently has a Risk Evaluation and Mitigation Strategies (REMS) consisting of a Medication Guide and Communication Plan. The data in this submission do not warrant a change to the approved REMS.

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

Exposure

A total of 188 PJIA patients received at least one dose of TCZ in Study WA19977 and are referred to by the applicant as the “all-exposure population.” At the time of the sBLA submission, mean duration of exposure to TCZ was approximately 1 year. Approximately one quarter of the patients who began on TCZ 10 mg/kg had changed dose regimen to 8 mg/kg due to increase in their body weight to the ≥ 30 kg category by the data cut-off for the original submission. Supportive safety data from MRA318JP and MRA319JP were summarized separately and included experience in 19 PJIA patients ranging from 3 to 19 years of age and treated with TCZ 8 mg/kg IV every 4 weeks with a total TCZ exposure of ~56 patient-years. Supportive safety data from the Japanese post-marketing safety registry ML21939 were also summarized separately and included 179 patients with an exposure of ~94 patient-years.

Deaths

No deaths were reported in the global PJIA program, including studies WA19977, MRA318JP, MRA319JP, or the Japanese post-marketing registry ML21939.

Serious Adverse Events

Table 8: Summary of Non-Fatal Serious AEs up to Week 16, Study WA19977

	BW <30 kg		BW ≥ 30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	35	34	119	188
TCZ Exposure, PY	11	10	36	58
No. of patients with ≥ 1 SAE, n (%)	2 (6%)	-	5 (4%)	7 (4%)
Total No. of events SAEs, n	2	-	6	8
Event by SOC and PT, n (% of patients)				
<u>Infection and Infestation</u>	<u>2 (6%)</u>	<u>=</u>	<u>2 (2%)</u>	<u>4 (2%)</u>
<i>Bronchitis</i>	2 (6%)	-	-	2 (1%)
<i>Cellulitis</i>	-	-	1 (1%)	1 (<1%)
<i>Pneumonia</i>	-	-	1 (1%)	1 (<1%)
<u>Gastrointestinal Disorders</u>	<u>=</u>	<u>=</u>	<u>1 (1%)</u>	<u>1 (<1%)</u>
<i>Constipation</i>	-	-	1 (1%)	1 (<1%)
<u>Nervous System Disorders</u>	<u>=</u>	<u>=</u>	<u>1 (1%)</u>	<u>1 (<1%)</u>
<i>Benign intracranial hypertension</i>	-	-	1 (1%)	1 (<1%)
<u>Hepatobiliary</u>	<u>=</u>	<u>=</u>	<u>2[†] (1%)</u>	<u>2[†] (<1%)</u>
<i>Cholangitis sclerosing</i>	-	-	1 (1%)	1 (<1%)
<i>Hypertransaminasemia</i>	-	-	1 (1%)	1 (<1%)

Source: Summary of Clinical Safety adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1; Table 40 of Dr. Nikolov’s review
 BW-body weight; PT-preferred term, PY- patient-years; SOC-system organ class, *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥ 30 kg and at least 5 kg over baseline weight for 3 consecutive visits; †-events are in one patient

Table 8 above summarizes the relatively few serious adverse events (SAEs) that occurred during the first 16 weeks of Study WA19977. Although data are not controlled, SAE by body

weight category and dose regimen can be compared. In this regard, the 10 mg/kg dose regimen appears to be similar to the 8 mg/kg dose regimen in the ≥ 30 kg weight category. The most common SAE were infection-related.

Because the trial is designed as a randomized withdrawal study, and TCZ has a long half-life and even longer pharmacodynamic effects, the controlled period is not very helpful in distinguishing between TCZ and placebo in the incidence of AEs and is not shown here. As per Table 9 below, safety data obtained over time in the study were consistent with the first 16 weeks in that the risk of TCZ 10 mg/kg dose regimen remained similar to the 8 mg/kg dose regimen in the >30 kg weight category and the most common SAE were infection-related.

Table 9: Summary of Non-Fatal SAE in Study WA19977, All Exposure Population, Through May 3, 2012 Data Cut-off

	BW <30 kg			BW ≥ 30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
No. of patients with ≥ 1 SAE, n (%)	4 (17%)	1 (8%)	3 (9%)	14 (12%)	22 (12%)
Total No. of events SAEs, n (rate per 100 PY)	4 (14)	1 (5)	3 (8)	20 (12)	28 (11)
Event by SOC and PT, n (rate per 100 PY)					
Infection and Infestation	3 (10.6)	1 (5.4)	2 (5.2)	6 (3.5)	12 (4.7)
<i>Pneumonia</i>	1 (3.5)	-	-	3 (1.8)	4 (1.6)
<i>Bronchitis</i>	2 (7.1)	-	-	-	2 (0.8)
<i>Cellulitis</i>	-	-	-	2 (1.2)	2 (0.8)
<i>Epstein-Barr virus infection</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Pyelonephritis</i>	-	1 (5.4)	-	-	1 (0.4)
<i>Varicella</i>	-	-	1 (2.6)	-	1 (0.4)
<i>Viral infection</i>	-	-	1 (2.6)	-	1 (0.4)
Injury, Poisoning, Procedural	-	-	-	3 (1.8)	3 (1.2)
Musculoskeletal/Connective Tissue	1 (3.5)	-	-	2[†] (1.2)	3 (1.2)
Congenital, familial, genetic (FMF)	-	-	-	2[†] (1.2)	2[†] (0.8)
Hepatobiliary	-	-	-	2[†] (1.2)	2[†] (0.8)
<i>Cholangitis sclerosing</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Hypertransaminasemia</i>	-	-	-	1 (0.6)	1 (0.4)
Eye Disorders	-	-	-	1 (0.6)	1 (0.4)
<i>Uveitis</i>	-	-	-	1 (0.6)	1 (0.4)
Gastrointestinal Disorders	-	-	-	1 (0.6)	1 (0.4)
<i>Constipation</i>	-	-	-	1 (0.6)	1 (0.4)
Nervous System Disorders	-	-	-	1 (0.6)	1 (0.4)
<i>Benign intracranial hypertension</i>	-	-	-	1 (0.6)	1 (0.4)
Respiratory/Thoracic/Mediastinal	-	-	-	1 (0.6)	1 (0.4)
<i>Asthmatic crisis</i>	-	-	-	1 (0.6)	1 (0.4)
Renal/Urinary tract	-	-	-	1 (0.6)	1 (0.4)
<i>Calculus urinary</i>	-	-	-	1 (0.6)	1 (0.4)
Psychiatric Disorders	-	-	-	1 (0.6)	1 (0.4)

Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp, staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1
 BW-body weight; PT-preferred term, PY- patient-years; SOC-system organ class, *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥ 30 kg and at least 5 kg over baseline weight for 3 consecutive visits; †-events are in one patient

Serious Infections

A total of 12 serious infections were reported through the data cut-off for the 120-day safety update (May 3, 2012) of Study WA19977. The types of serious infections observed are consistent with the TCZ experience to date. No opportunistic infections were observed in Study WA19977, MRA318JP or MRA319JP. All patients were screened for latent tuberculosis (TB) infection at baseline and Week 52 of Study WA19977. No cases of TB reactivation were reported, and one patient from an endemic area developed primary pulmonary TB in Study WA19977 and MRA318/319JP.

Malignancy

Immunosuppressive products raise a theoretical concern for an increased risk of malignancy due to decreased immunosurveillance. Malignancies have been observed in the adult RA program, but do not appear to be occurring at rates that are above the range of background rates. No malignancies have been observed thus far in the global PJIA database including Study WA19977, MRA318JP, MRA319JP or ML21939, but uncommon events of longer latency, such as malignancy, may not yet be manifested in the limited experience thus far.

Gastrointestinal Perforations

There were no events of gastrointestinal (GI) perforations reported in Study WA19977, MRA318JP/319MP. One case of a perforated gastric antral ulcer was reported in a patient with PJIA who was also using ibuprofen.

Hypersensitivity and Anaphylaxis

Anaphylaxis, including fatal events, has been reported with the adult RA pre- and post-marketing experience. In the PJIA development program, including Study WA19977 and MRA318/319JP, no cases of hypersensitivity or anaphylaxis (defined by Sampson's criteria³) were reported. In addition, no events with the preferred term of hypersensitivity were reported during the study. There were two patients, each in study WA19977 and MRA319JP who tested positive for neutralizing anti-tocilizumab antibodies; however this was not associated with hypersensitivity, anaphylaxis, or clinically significant infusion reactions.

Discontinuations due to Adverse Events

Discontinuations due to AEs are summarized in Table 10 below. Generally, discontinuations occurred at a higher rate in the <30 kg body weight category, albeit at the same rate in the 8 and 10 mg/kg dose regimen subgroups in that category. This is consistent with other PJIA development programs, in that the youngest, smallest children have the most severe disease. The AEs leading to discontinuation were a subset of the SAE observed in the study.

³ Sampson HA, et al. Second symposium on the definition of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. JACI 2006;117(2):391-7

Table 10: Summary of Adverse Events Leading to Discontinuation from Study WA19977

	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
AEs leading to withdrawal, n (rate per 100 PY)	2 (7.1)	-	2 (5.3)	3 (1.8)	7 (2.7)
Scleroderma†	1 (3.5)	-	-	-	1 (0.4)
Hypertransaminasemia†	-	-	-	1 (0.6)	1 (0.4)
Serum sickness-like reaction	-	-	1 (2.6)	-	1 (0.4)
Pneumonia	-	-	-	1 (0.6)	1 (0.4)
Blood bilirubin abnormal	1 (3.5)	-	-	-	1 (0.4)
Juvenile arthritis flare	-	-	1 (2.6)	-	1 (0.4)
Benign intracranial hypertension†	-	-	-	1 (0.6)	1 (0.4)

Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1; Table 43 of Dr. Nikolov's review.
 BW-body weight; PY- patient-years; *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits; †-SAEs

Common Adverse Events

As summarized in Table 11 below, the most common adverse events occurring in tocilizumab-treated PJIA patients in Study WA19977 were disease flares, nasopharyngitis/pharyngitis, headache, upper respiratory infection, cough, and GI symptoms including nausea, vomiting, and diarrhea. These types of events are consistent with the most common AEs in the adult RA and SJIA trials.

Table 11: Common AEs (>5%) in Study WA19977, by Preferred Term, data cut-off November 4, 2011

	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	28	7*	34	119	188
TCZ Exposure, PY	23	9	25	120	177
Duration in study, PY	25	9	27	124	184
PT term, No. of patients (%)					
Juvenile arthritis	6 (21)	2 (29)	6 (18)	35 (29)	49 (26)
Nasopharyngitis	6 (21)	-	5 (15)	28 (24)	39 (21)
Headache	3 (11)	-	5 (15)	18 (15)	26 (14)
Upper respiratory tract infection	2 (7)	-	3 (9)	14 (12)	19 (10)
Cough	2 (7)	2 (29)	3 (9)	11 (9)	18 (10)
Pharyngitis	3 (11)	-	2 (6)	12 (10)	17 (9)
Nausea	-	-	2 (6)	14 (12)	16 (9)
Diarrhea	1 (4)	-	2 (6)	11 (9)	14 (7)
Rhinitis	2 (7)	1 (14)	4 (12)	7 (6)	14 (7)
Vomiting	1 (4)	1 (14)	3 (9)	9 (8)	14 (7)
Abdominal pain	1 (4)	1 (14)	2 (6)	9 (8)	13 (7)
Oropharyngeal pain	1 (4)	-	2 (6)	10 (8)	13 (7)
Rash	1 (4)	-	3 (9)	6 (5)	10 (5)
Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1; stae13_ae; Table 47 of Dr. Nikolov's review. BW-body weight; PY- patient-years; SOC-system organ class, *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits					

Laboratory abnormalities

Tocilizumab treatment has effects on hepatobiliary, hematologic, and lipid laboratory parameters. These abnormalities have previously been described and explored in detail in the original clinical review and clinical review of the complete response for BLA 125276. The data in this submission are consistent with previously described effects of tocilizumab on these laboratory parameters. To summarize:

1) Hepatobiliary abnormalities

Consistent with its mechanism of action (IL6 inhibition via binding of cell surface IL6 receptors), tocilizumab treatment is associated with reversible elevation in hepatobiliary parameters. Hepatocytes express high levels of IL6 receptor, and IL6 drives hepatic production of acute phase reactants. As discussed in the original BLA, although the mechanism of action of tocilizumab-mediated hepatobiliary laboratory abnormalities has not been elucidated, there are plausible mechanisms by which these might occur. First, IL6 appears to have a hepatoprotective effect on various forms of liver injury and promotes hepatocyte regeneration. Therefore inhibition could lead to increased hepatocyte susceptibility to hepatotoxic insults. Less likely, since tocilizumab does not induce significant effector

function, is the possibility that tocilizumab binding on hepatocyte surface IL6 receptors could result in some complement-mediated cytotoxicity, or antibody-dependent cellular cytotoxicity.

Thus far, these abnormalities do not appear to be correlated with clinical hepatotoxicity, and are reversible with discontinuation of treatment. In adult RA, approximately 50% of patients treated with tocilizumab experienced elevations in AST or ALT up to 3 times the upper limit of normal (ULN). A small percentage (1 to 7%) of patients experienced elevations from 3 to 5 x ULN, and yet smaller proportions (1 to 2%) experienced elevations from 5 to 8 x ULN.

A similar pattern is noted with TCZ treatment in the PJIA population, particularly with more extended treatment. Approximately 30% of patients experienced elevations of ALT and/or AST up to 2.5 x upper limit of normal [ULN](Grade 1), 5% with elevations up to 5 x ULN (Grade 2), and up to 2% with elevations between 5 and 20 x ULN (Grade 3). No patients met criteria for Hy's Law (transaminase elevation >3 x ULN + bilirubin elevation >2 x ULN without evidence of biliary obstruction). These data are generally consistent with the hepatobiliary safety profile of TCZ in adult RA and SJIA.

2) Hematologic abnormalities

IL6 is an essential hematopoietic growth factor; therefore its inhibition can result in reduction in white blood cells and platelets. Up to 20% of adult RA patients treated with tocilizumab experience Grade 1 or Grade 2 neutropenia, however few experience more severe neutropenia. Neutropenia is reversible with discontinuation of treatment. In the adult RA clinical trial experience, this neutropenia has more often not been associated with clinical adverse events.

Approximately 25% of PJIA patients treated with TCZ also experienced Grade 2 or higher neutropenia during Study WA19977 through the data cut-off for the submission. Similar to the adult experience, most cases of neutropenia were not associated with clinically significant infections.

Similarly, mild thrombocytopenia associated with tocilizumab treatment is not uncommon (approximately 10% incidence), but has been associated with very few clinical adverse events and is reversible with discontinuation of treatment.

3) Lipid abnormalities

In adults, TCZ treatment has been associated with an increase in all lipid parameters—average increases of 30 mg/dl in total cholesterol, 20 mg/dl in LDL, 5 mg/dl in HDL, and 30-40 mg/dl in triglycerides. In general, LDL increases take place by Week 6 and do not increase further with successive TCZ treatment over time. These increases are reversible with discontinuation, and are also amenable to treatment with lipid-lowering agents. The rates of cardiovascular adverse events in the RA TCZ clinical development program have been lower than published background rates in RA. Nonetheless, with tocilizumab's approval, a controlled cardiovascular outcomes study has been enacted as a postmarketing requirement in order to attempt to more definitively describe the effect that these lipid abnormalities may have on patients receiving tocilizumab long-term.

Approximately 5-10% of patients in Study WA19977 developed mild total cholesterol elevation (up to 1.5 x ULN) and less than 5% developed mild LDL elevation (up to 1.5 x ULN). No patients experienced elevation in either total cholesterol or LDL cholesterol over 2 x ULN. Overall the lipid abnormalities in WA19977 are consistent with those observed in the adult RA and SJIA populations.

- **Immunogenicity**

In study WA19977, all patients were tested at baseline and other selected timepoints for anti-TCZ antibodies. Patient samples were initially tested by a screening assay and, if positive, these samples were subsequently tested with the confirmatory assay. If patient samples were positive for the confirmatory assay, the samples were further assessed for anti-TCZ neutralizing antibodies.

However, as noted in Section 3, an updated immunogenicity assay was used in the study and the applicant was requested to describe any differences between this assay and the one used for the original BLA (RA indication). Although there were minor quantitative differences between the assays, the primary product quality reviewer, Dr. Gerald Feldman, concluded that any differences between the assays would not change the overall results or interpretation of results.

Almost all patients (187/188, 99.5%) enrolled in study WA19977 were tested with the screening assay. Of these, 20 patients (10.6%) had positive baseline anti-TCZ assay results, 3 (1.6%) had positive screening assay results post-baseline, and 1 had positive confirmation and neutralizing assay results post-baseline (0.5%). This patient developed the anti-TCZ neutralizing antibodies at Week 20 but did not experience any clinical adverse effects. In MRA318/319JP, one patient became positive for neutralizing antibodies before the fourth infusion and became positive for IgE antibodies after the fifth infusion 657 days later and was withdrawn from the study, although no clinical adverse effects were associated.

In adults, the incidence of positive immunogenicity assay results was approximately 2% (46/2876) patients in the Roche RA clinical program, of whom 5 had an associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies. A higher proportion of patients developed anti-TCZ HAHAAs after exposure to TCZ 4 mg/kg + MTX compared with 8 mg/kg TCZ + MTX. Based on a limited number of cases, anti-TCZ antibodies or neutralizing antibodies did not appear to impact on the safety and/or efficacy of TCZ.

- **Special safety concerns**

GI Perforations

In the adult RA program, gastrointestinal perforation with TCZ treatment appeared to be increased over expected background rates. No gastrointestinal perforation cases have been reported to date in study WA19977 or in MRA318/319JP. One case of a perforated gastric

antral ulcer was reported in the post-marketing setting, in a patient who was also receiving concomitant ibuprofen.

Infusion reactions

Infusion reactions were not systematically evaluated in Study WA19977, other than classifying adverse events as occurring during infusion or within 24 hours of infusion. Premedication was not pre-specified in the protocol, however medications to treat hypersensitivity reactions and anaphylaxis were available at infusion sites.

The most common AEs occurring during infusion were hypotension, nausea, and headache, which all occurred at approximately 2 events per 100 patient-years of exposure. Overall, 11/188 (6%) patients experienced at least one AE during infusion. Up to 20% of patients experienced an AE within 24 hours of infusion. The most common AEs occurring within 24 hours of infusion were dizziness, hypotension, nausea, and pyrexia.

Comparative Safety Profile

Table 12 summarizes the major safety events across the tocilizumab PJIA, adult RA, and SJIA clinical trials. The marked difference in exposure between the adult and pediatric programs and differences between the diseases (e.g., SJIA patients being more severely ill) limits the ability to draw conclusions. However, in terms of deaths, SAE (including serious infection), and discontinuation due to AEs, rates in the PJIA population appear to be consistent with the adult RA population, and lower than for SJIA. This is consistent with what might be anticipated, based on historical experience with these disorders.

Table 12: Comparative Safety Summary in PJIA, Adult RA, and SJIA

	PJIA	Adult RA	SJIA*
N	188	4009	112
Exposure, PY	184	14993	202
Number of patients/events (rate per 100-PY)			
All AEs	159/885 (480)	3799/45198 (301)	111/1660 (822)
<i>Infections and infestation</i>	115/302 (164)	3077/14112 (94)	102/570 (282)
<i>Gastrointestinal disorders</i>	60/131 (71)	2072/5467 (37)	67/145 (72)
Deaths	0	85 (0.6)	3 (1.5)
SAEs	17/23 (13)	1255/2194 (15)	35/47 (23)
<i>Serious infections</i>	9/9 (5)	507/668 (5)	20/22 (11)
AEs leading to withdrawal	6/6 (3)	749/754 (5)	6/6 (3)
<small>Source: Summary of Clinical Safety, Adapted from Tables 24 and 25 and 120-day safety update; Table 59 of Dr. Nikolov's review *the clinical data cut-off for the sJIA program is as of May 31, 2011, the two-year data from the ongoing study WA18221</small>			

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

Dr. Nikolov has concluded that the types and rates of adverse events submitted with this supplement are generally consistent with those reviewed with the original BLA and has not

identified any new safety signals. The safety profile of tocilizumab in PJIA appears to be similar to the safety profile of tocilizumab in adult RA and provides for an acceptable risk:benefit balance in this population.

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

I concur that the safety profile, and risk:benefit balance, of tocilizumab for PJIA is acceptable. However, I am also of the opinion that uncommon adverse events or adverse events of longer latency would likely be missed in the relatively limited patient numbers and duration of exposure available for review in this application. Therefore I recommend a post-marketing requirement for additional long-term safety data, as described in Section 13 below.

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

Notable issues are described above.

9. Advisory Committee Meeting

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

10. Pediatrics

This application was discussed at the Pediatric Review Committee (PeRC) meeting on February 6, 2013. Study WA19977 was conducted as a PREA requirement (for the RA approval) and under a special protocol assessment (SPA) agreement. As per the PREA requirement from the original BLA approval, this study was required to assess the pharmacokinetics, dosing, efficacy, safety, tolerance and immunogenicity of polyarticular JIA patients ages 2 to <17 years, and has done so. Therefore I recommend this postmarketing requirement (PMR) be designated as fulfilled.

Data from the ongoing 64-week open label extension period of Study WA19977 will be submitted as part of the requirements of a Written Request issued for tocilizumab on November 15, 2012. The other studies in the Written Request include a PK/safety study of IV tocilizumab in SJIA patients under 2 years of age (PREA requirement from the SJIA approval), a study of the PK, pharmacodynamics (PD), and safety of subcutaneous tocilizumab in patients with SJIA 2 to 17 years of age, and a study of the PK, PD, and safety of subcutaneous tocilizumab in PJIA patients 2 to 17 years of age.

The sponsor received orphan designation for the PJIA indication on July 31, 2012, thus new PREA requirements are not triggered by this new indication.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**—No issues.
- **Financial disclosures**—Acceptable.
- **Other GCP issues**—Not applicable.
- **DSI audits**—DSI inspection was not warranted in this case for the following reasons:
1) the product is already approved, 2) any specific individual site contained so few patients that it would be unlikely to affect overall results, and 3) the treatment effect size was large, again suggesting that inspection of 2 or 3 clinical sites would not be likely to affect overall conclusions.
 - **Other discipline consults**—None requested.
 - **Any other outstanding regulatory issues**—None identified.

12. Labeling

- **Proprietary name**—No issues, already approved.
- **DDMAC, DMEPA and OSE Division comments**—These were relatively minor, given that these Divisions have extensively reviewed and commented on the label with the original approval and SJIA approval. The proposed changes to the label were also limited to the addition of the PJIA data, primarily in the indications, dosage and administration, Section 6 and Section 14.
 - **Physician labeling**
The primary proposed changes included the addition of the PJIA indication and dosing regimen to those respective sections of the label, along with clinical data in PJIA patients for Section 6 Adverse Reactions, Section 12.3 Pharmacokinetics, and Section 14 Clinical Studies. The review team recommended the addition of data from Part I and II of the study regarding responses by concomitant MTX use, to convey the apparently additive beneficial effect of MTX. The review team also deleted a proposed (b) (4), as this would be difficult for clinicians to interpret in light of the randomized withdrawal design. Instead, Part I response data was included, and Part II data were limited to the primary endpoint (proportion of patients with JIA ACR30 flare).
- **Carton and immediate container labels (if problems are noted)**—No issues.
- **Patient labeling/Medication guide (if considered or required)**—The Medication Guide and patient labeling were revised to include reference to the PJIA indication.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this efficacy supplement, provided agreement can be reached with the applicant on revisions to the proposed label and postmarketing requirements.

- **Risk Benefit Assessment**

The risk:benefit profile of tocilizumab in PJIA appears to be favorable. The risks of tocilizumab treatment in this patient population appear to be qualitatively similar as those seen in adults with RA; with the primary serious risk being an increased risk of infection. Abnormalities in hepatobiliary, hematologic, and lipid parameters were also observed in PJIA patients; however, as with adults, these abnormalities did not appear to be correlated with clinical adverse events. However, the risks of tocilizumab are not minimal, and IL6 has physiological functions in immune and skeletal system development. Therefore additional long-term data should be obtained to ensure the risk-benefit profile remains favorable with long-term TCZ treatment.

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

The currently approved REMS for Actemra consists of a communication plan. No new safety signals were identified in this submission, therefore no change to the currently approved REMS is warranted on the basis of the data in this submission.

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

In considering whether a postmarketing requirement should be enacted, I considered the following factors:

- Tocilizumab would be the first IL6 inhibitor approved for PJIA
- The application contains limited data on the long-term safety of tocilizumab in patients with PJIA
- Unlike the situation with SJIA, there are a number of effective therapeutic options for PJIA
- IL6 has physiological functions in immune and skeletal system development
- Existing knowledge of the effects of IL6 blockade on growth and development are limited to knock out mice models and juvenile rat studies using a murine anti-IL6R antibody⁴.

Therefore to ensure the long-term risk-benefit profile of tocilizumab in PJIA remains favorable, safety should be further assessed by a long-term safety study with inclusion of a control group, to evaluate for malignancies, serious infections, gastrointestinal perforation, and effects on growth.

- **Recommended Comments to Applicant—None.**

⁴ Sakurai T et al., "The effects of interleukin-6 signal blockade on immune system, reproductive and skeletal development in juvenile mice." Birth Defects Research (Part B) 00:1-13 (2013)

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/s/

SARAH K YIM
04/08/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type Supplemental BLA
Application Number(s) 125,276/64
Priority or Standard Standard

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Reviewer Name(s) Nikolay P. Nikolov, M.D.
Review Completion Date March 25, 2013

Established Name Tocilizumab
(Proposed) Trade Name Actemra[®]
Therapeutic Class Interleukin-6 (IL-6) Inhibitor
Applicant Hoffmann-LaRoche

Formulation(s) Intravenous (IV)
Dosing Regimen 8 or 10 mg/kg every 4 weeks
Indication(s) Polyarticular Juvenile
Idiopathic Arthritis (pJIA)
Intended Population(s) Active pJIA

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this efficacy supplement with revisions to the proposed labeling as outlined in section Labeling Recommendations. I further recommend that the pivotal study WA19977 is considered to have fulfilled the requirement under Pediatric Research Equity Act (PREA) as set forth in the approval letter of the original BLA, January 08, 2010.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The current efficacy supplement was submitted to provide data in support of the use of tocilizumab (Actemra®) for the following indication:

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

If approved, tocilizumab will be the fourth biologic, and the first in class of IL-6 targeting therapeutics approved for the proposed indication in the US.

The pivotal data for this application are derived from a single PREA-required study (WA19977) conducted under a special protocol agreement. This is an ongoing three-part Phase 3 study to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in patients with active pJIA. The targeted population consisted of pediatric patients who had shown an inadequate response to MTX or were intolerant to MTX. However, concomitant MTX was permitted and used by approximately 80% of patients during the study. The study consisted of the following three periods:

- Part I (complete) was a 16-week open-label TCZ treatment lead-in period:
 - All patients weighing at least 30 kg received 8 mg/kg TCZ IV every 4 weeks (q4w).
 - Patients weighing less than 30 kg were randomized in a 1:1 ratio to either 8 mg/kg or 10 mg/kg TCZ q4w.
 - Efficacy was assessed using the JIA American College of Rheumatology (ACR) response measure. Patients who achieved at least a 30% improvement (i.e., a JIA ACR30 response) at week 16 compared to baseline were eligible to enter Part II.

Data from this period of the study provided short-term (16 weeks) evidence of relative safety and efficacy between the two studied dosing regimens 8 mg/kg (n=34) or 10 mg/kg (n=35) TCZ q4w in patients weighing less than 30 kg.

- Part II (complete) was a 24-week randomized, double-blind, placebo-controlled withdrawal period in which patients were randomized in a 1:1 ratio to treatment with TCZ at the same dose level as in Part I or to placebo. Randomization was stratified by concomitant MTX use and concomitant oral corticosteroid use. Patients who developed a JIA ACR30 flare relative to week 16 qualified for escape therapy with TCZ at the same dose as in Part I. The data from this period of the study provided the primary evidence of efficacy.
- Part III (ongoing) is a 64-week open-label period beginning at week 40 (or once a patient entered escape therapy with TCZ) to examine the long-term use of TCZ on safety and efficacy. In patients originally randomized to the TCZ 10 mg/kg dose, the investigator had the option to reduce the TCZ dose level to 8 mg/kg if the patient's body weight had increased to ≥ 30 kg and was at least 5 kg above the baseline weight for three consecutive visits. Part III is ongoing. The last patient's last visit is expected for January 2013.

Supportive efficacy and safety data were provided by the Japanese studies MRA318JP and MRA319JP in 19 pJIA patients and additional safety data were derived from the postmarketing Japanese surveillance program and spontaneous reporting in pJIA, sJIA, unspecified JIA and unspecified indications in the pediatric populations exposed to tocilizumab.

Summary of Efficacy

The clinical efficacy data are derived from one study, WA19977 conducted under a special protocol (SPA) agreement. The acceptability of a single study to support the proposed additional claims, following the approval of the original BLA, is consistent with a prior precedent of relying on single studies for pJIA indication in the context of established efficacy in adult RA. The endpoints to support the proposed claim were also precedented.

The primary endpoint in study WA19977 was defined as the proportion of patients who develop a Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology (ACR) 30 flare (relative to Week 16) in study Part II (i.e. by Week 40). The ITT population was used for the primary endpoint assessment as pre-specified. A total of 13 secondary endpoints with pre-defined hierarchical order were selected by the applicant for Week 40 analyses.

Results from the statistical analyses using the pre-specified statistical analysis plan are summarized below:

- The study met its primary efficacy endpoint at week 40 with 48.1% of patients receiving placebo experiencing a JIA ACR30 flare between weeks 16 and 40 compared to 25.6% of patients receiving TCZ (p=0.0024). The clinical efficacy results from the primary analysis demonstrate a statistically significant and clinically meaningful difference between the two groups providing evidence of efficacy of tocilizumab in treating patients with active polyarticular JIA.
- Analyses of the major secondary endpoints and sensitivity analyses are consistent with the primary analyses, including:
 - Improvement in the JIA ACR core components
 - Improvement in JIA ACR 30/50/70 response rates at both Week 16 (the end of the open-label lead-in period) and Week 40 (the end of the placebo-controlled randomized withdrawal period)

Further, the efficacy analyses indicate a numerically better efficacy for the proposed dosing of 10 mg/kg as compared with 8 mg/kg every 4 weeks for the patients with body weight lower than 30 kg, as measured by the JIA ACR flare rate following randomized withdrawal and JIA ACR30/50/70/90 response rates, supporting the proposed dosing recommendation:

- 8 mg/kg every 4 weeks for patients with a body weight \geq 30 kg
- 10 mg/kg every 4 weeks for patients with a body weight < 30 kg

The use of stable doses of methotrexate (MTX) at baseline was allowed but not required in the protocol and was pre-defined stratifications variable. Approximately 79% of patients were taking MTX at baseline. Subpopulation analyses comparing efficacy between patients taking and those not taking MTX suggested that background MTX provided additional clinical benefit independent of that of tocilizumab.

The clinical efficacy results from the supporting Japanese studies MRA318/319JP were consistent with the results from Study WA19977.

The efficacy analyses and interpretation of the results conducted by the FDA's statistical review team and reviewed in detail in a separate document are in general agreement with the analyses performed by the sponsor.

Summary of Safety

The safety data reviewed for this efficacy supplement were derived from the following sources:

- The registration study WA19977 which is an ongoing three-part Phase 3 study to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in patients with active pJIA. In this study MTX use was allowed but not required as background therapy.
- Supportive Japanese studies MRA318JP and MRA319JP which are open-label tocilizumab monotherapy studies in 19 patients with active pJIA.

- Japanese postmarketing study ML21939 for pJIA and adult RA
- Japanese postmarketing study ML21940 for sJIA
- Spontaneous reports received globally, including those from non-interventional studies for patient treated for pJIA, sJIA, JIA that are unspecified by classification, and in pediatric patients under the age of 18 years treated with tocilizumab for unknown indications. Importantly 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 reported as of July 31, 2012.

The duration of exposure in this pediatric program is relatively small; however the overall extent and duration of exposure are generally comparable with the exposure in pJIA development programs of already approved products and meets the Division's expectations of a safety database and exposure to allow for a qualitative assessment of safety in the context of previously defined safety profile of tocilizumab in adult RA.

Based on the known safety profile of tocilizumab in adult RA patients and patients with sJIA, primary AEs of interest included infections, neutropenia, liver function test abnormalities, anaphylaxis and gastrointestinal perforations.

The review of the clinical safety data indicates that the main areas of safety concern remain consistent with the previously defined safety profile of tocilizumab and are as expected for the morbidities in the studied patient population:

- No new safety signals have been identified in pJIA program
- The types of AE and SAEs are expected for the underlying patient population and consistent with the findings in adults with RA
- Infections AEs were the most frequent AEs in pJIA population with incidence higher than that in adult RA population, 480 vs. 301 events per 100 patient years respectively. This is reflective of the more common respiratory tract infections in the pediatric population. The incidence rates of serious infections in pJIA were comparable to those of the adult RA population (5 events per 100 patient years in both programs). No opportunistic infections were reported in pJIA development program.
- No malignancies were reported in the pJIA development program.
- No gastrointestinal (GI) perforations were reported in study WA19977 and the supporting Japanese studies MRA318/319JP. In the post-marketing setting, one case of a perforated gastric antral ulcer was reported in pJIA; the case was confounded by concomitant ibuprofen use. GI perforations are labeled events.
- The laboratory abnormalities and outcomes are also consistent with the incidence and severity of abnormalities in prior submission and are labeled events. No cases met Hy's law criteria.
- Immunogenicity was prospectively assessed in the pJIA program. There were two patients, each in study WA19977 and MRA319JP, who tested positive for neutralizing anti-tocilizumab antibodies; however this was not associated with

hypersensitivity, anaphylaxis, clinically significant infusion reactions, or loss of efficacy.

- No cases of hypersensitivity or anaphylaxis (defined by Sampson's criteria¹) were reported in study WA19977 and the supporting Japanese studies MRA318/319JP. Cases of non-fatal anaphylaxis were reported in the post-marketing setting. Hypersensitivity, including anaphylaxis are labeled events.
- No deaths occurred in the registration trial WA19977, the supportive Japanese studies MRA318/319/JP or the Japanese post-marketing surveillance study.

With respect to dose-dependency, the relatively small number and the nature of the SAEs and serious infections (as the most common SAE), do not indicate a clear dose-dependent increases between the 10 mg/kg and 8 mg/kg dose regimens in patients with body weight less than 30 kg.

The overall safety results from the supporting Japanese studies MRA318/319JP were consistent with the results from Study WA19977.

Risk Benefit Assessment

The current submission provides evidence of tocilizumab's clinical efficacy in reducing the signs and symptoms of disease and reducing disease flare rates in patients 2 to <17 years of age with active polyarticular JIA. Tocilizumab treatment of this patient population provided a statistically significant and clinically meaningful benefit in reducing the signs and symptoms of the disease and reduction in the disease flare rates compared to placebo. No new safety signals for tocilizumab have been identified in pJIA compared with adult RA population. Therefore, the overall risk-to-benefit profile of tocilizumab is favorable in the population of patients with active polyarticular JIA.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Tocilizumab currently has a REMS consisting of a Medication Guide and Communication Plan. Based on this submission, I believe the current REMS remains adequate.

1.4 Recommendations for Postmarket Requirements and Commitments

Based on this submission, I do not have specific recommendations for additional post-marketing requirements and commitments. Furthermore, following the submission of

¹ Sampson HA, et al. Second symposium on the definition of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. JACI 2006;117(2):391-7

this application, the sponsor was granted orphan designation for the proposed indication.

2 Introduction and Regulatory Background

Polyarticular course juvenile idiopathic arthritis (pJIA) is one of seven widely accepted subsets of the larger group of JIA defined by International League of Associations for Rheumatology (ILAR)². The category of oligoarthritis is further divided into persistent oligoarthritis and extended oligoarthritis with the latter category following the course of polyarticular JIA.

Table 1. Summary of ILAR Categories of Juvenile Idiopathic Arthritis (JIA)

Summary of ILAR Categories of Juvenile Idiopathic Arthritis (JIA)			
Subset	Frequency	Onset age	Gender ratio
Systemic JIA	4-17%	Throughout childhood	F = M
Oligoarticular	27-56%	Early childhood, peak 2-4 years	F >>> M
RF-positive polyarthritis	2-7%	Late childhood or adolescence, peak 10-14 years	F >> M
RF-negative polyarthritis	11-28%	Biphasic, early peak at 2-4 years, later peak at 6-12 years	F >> M
Enthesitis-related arthritis	3-11%	Late childhood or adolescence	M >> F
Psoriatic arthritis	2-11%	Biphasic, early peak at 2-4 years, later peak at 9-11 years	F >> M
Undifferentiated arthritis	2-15%		
RF-rheumatoid factor			

The clinical development program under review in this supplement has targeted a patient population with rheumatoid factor (RF) positive, RF-negative and extended oligoarticular JIA which is comparable to the patient population studied in development programs of already approved biologic therapies for JIA and is regarded as the pediatric equivalent of adult RA. The confirmatory study WA19977 was conducted under a Special Protocol Agreement and is intended to fulfill PREA requirements as set forth in the original BLA approval letter.

² Ravelli A and Martini A. Juvenile Idiopathic Arthritis Lancet. 2007;369: 767-78.

2.1 Product Information

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). Tocilizumab selectively binds to soluble and membrane-bound human IL-6R, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6. The data obtained from in vitro assays demonstrate that tocilizumab has essentially no or minimal complement dependent cytotoxicity (CDC) activity and little or no significant antibody dependent cellular cytotoxicity (ADCC) activity. The molecular mass of the protein moiety of the antibody is approximately 145 kDa.

It is the first in class (targeting IL-6 signaling pathway) biologic agent for treatment of adult patients with rheumatoid arthritis and pediatric patients with systemic juvenile idiopathic arthritis approved in the United States.

2.2 Tables of Currently Available Treatments for Proposed Indications

The classes of therapies for pJIA include non-steroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs). The most widely accepted traditional DMARD for the treatment of pJIA is methotrexate because of its proven potency and well understood long-term effects. Biologic DMARDs have revolutionized the treatment of adult rheumatoid arthritis (RA) over the past two decades and some have since been successfully used in the management of pJIA. Among all of these available therapies however, only three products have been approved for the treatment of pJIA in the United States as listed in Table 2, two TNF-inhibitors, adalimumab and etanercept, and one targeting T-cell co-stimulatory signaling pathway, abatacept.

Table 2. Approved Products for Treatment of pJIA in the United States

Product Name (Trade Name) [Sponsor] {year initial approval/ pJIA approval}	Presentation and ROA [†]	Description and MOA [§]
Etanercept (ENBREL) [Immunex/Amgen] {1998/2008}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL <i>SC injection</i>	Fusion protein consisting of TNF-R and human IgG1 Fc <i>TNF inhibitor</i>
Adalimumab (HUMIRA) [Abbott] {2002/2008}	Prefilled syringe 40 mg/0.8 mL Humira Pen 40 mg/0.8 mL <i>SC injection</i>	Human IgG1 k mAb <i>TNF inhibitor</i>
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005/2008}	Lyophilized powder 250 mg/vial <i>IV infusion</i>	Fusion protein consisting of CTLA-4 and human IgG1 Fc <i>T cell activation inhibitor</i>

If approved, tocilizumab will be the first in class of drugs targeting IL-6 signaling pathway for the treatment of patients with pJIA. Tocilizumab has already been approved

for the treatment of another subset of childhood arthritides, systemic JIA (sJIA) in April 2011.

2.3 Availability of Proposed Active Ingredient in the United States

Tocilizumab is commercially available in the United States since its FDA approval on 01/08/2010.

2.4 Important Safety Issues With Consideration to Related Drugs

Tocilizumab is the first in class IL-6 signaling inhibitor. Therefore, the safety profile of IL-6 inhibition is based on the information submitted in the original and the supplemental BLAs, and anticipated effects based on currently available knowledge about the biological effects of IL-6 and the clinical trial experience with tocilizumab. Based on this information, the primary issues of concern pertain to:

- Overall immunosuppression and the risk for serious infection.
- Liver enzyme abnormalities and concern that this could result in clinically evident hepatotoxicity.
- Reduction in white blood cell counts and incumbent risk for infection from this.
- Elevated lipids with whatever long-term ramifications this may have on cardiovascular risk. As IL-6 is the primary driver of acute phase reactants, and inflammation is associated with increased cardiovascular risk, it is also possible that inhibition of IL-6 may be beneficial with respect to cardiovascular risk.
- Potential promotional effect on certain malignancies as suggested by basic science literature. However, the clinical trial evidence thus far suggest a neutral effect with respect to tocilizumab treatment and malignancy overall.
- Gastro-intestinal perforations have been identified as a potential safety signal in the clinical development program and are prospectively monitored by the applicant and reported as part of the Periodic Adverse Event Reporting.

The supplemental BLA safety update indicates an overall tocilizumab safety profile consistent with that reviewed in the original BLA. No new safety signals have been identified.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of the presubmission regulatory history related to this submission is presented below:

- September 21, 2004: pre-IND meeting
- March 20, 2007: EOP2 meeting held focusing on proposed clinical studies for both sJIA and pJIA.
- November 17, 2008: SPA request was submitted for WA19977 but denied due to Agency concerns regarding the stratification and statistical analysis, the handling

of missing values, endpoint multiplicity, and patient population. These concerns were addressed during a Type A meeting with Sponsor on March 5, 2009.

- June 08, 2009: Based on the protocol revisions following the Type A meeting discussion, a Special Protocol Agreement was reached. At the time, the Agency indicated that WA19977, if successfully conducted, would be adequate to fulfill the PREA requirements for the initial approval of TCZ in adult RA patients. In addition, a positive outcome of this study could be used to support an sBLA filing for the indication of pJIA.
- January 08, 2010: Original BLA for the treatment of adult patients with RA was approved. In the approval letter to address PREA requirements, the Agency:
 - Waived the pediatric studies requirement for ages 0 to <2 years because juvenile idiopathic arthritis (JIA) polyarticular subtype most often occurs in children ages ≥ 2 years and older and is infrequent in children ages 0 to < 2 years.
 - Deferred submission of pediatric study for ages ≥ 2 to < 17 years.
 - Assessment of pharmacokinetic (PK/PD) parameters and dosing, efficacy, safety, tolerance and immunogenicity in the pediatric population ages ≥ 2 years to < 17 years with polyarticular JIA. (The letter was referring to study WA19977 which was under way)
- May 01, 2012: pre-sBLA written responses were provided to Sponsor. The Agency agreed that proposed safety and efficacy data appeared adequate to support filing of the application for pJIA indication. In addition, the Agency recommended comparison of pJIA safety data to overall tocilizumab safety, including safety in adult RA.

The current submission is an efficacy supplement (#64) to the BLA to address the PREA requirement for the original approval for adult RA and to provide safety and efficacy data in support of the proposed indication:

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

A detailed regulatory history of the overall BLA application is presented below:

The original biologic license application (BLA) for tocilizumab in rheumatoid arthritis (RA) was submitted November 19, 2007, and received a complete response on September 17, 2008, due to deficiencies in the nonclinical program and on inspection of the manufacturing facilities. The clinical efficacy data submitted in the original BLA were derived from 5 randomized, double-blind, controlled trials of TCZ in 4211 RA patients with moderately to severely active disease. These data provided substantial evidence of the efficacy of TCZ for the treatment of RA. The safety data submitted, which included approximately 4700 patients and over 7900 patient-years of exposure in the global safety database, were consistent with the profile of an immunosuppressant, with an increased risk of serious infections. Likely related to mechanism of action, TCZ

treatment also resulted in abnormalities of laboratory parameters, including decreased white blood cell count, increases in lipids, and liver enzyme elevations, although these were not associated with serious clinical adverse events in the controlled setting of the clinical trial experience. Malignancies, GI perforations, and demyelinating adverse events were observed in the clinical trials; however the relative risk and role of TCZ treatment in the development of these adverse events was not well-defined. Overall, the risk:benefit profile of TCZ in RA appeared to be favorable based on these clinical data.

A meeting of the Arthritis Advisory Committee (AAC) was convened on July 29, 2008 to discuss the clinical data in the original tocilizumab BLA submission. The members of the committee concurred that efficacy was demonstrated in RA. They were uncertain whether the data clearly indicated a benefit of 8 mg/kg over the 4 mg/kg dose in patients with an inadequate response to DMARDs, as some members noted that the components of the ACR response criteria showed little difference between doses with the exception of effect on C-reactive protein (CRP) levels. The risk of serious infection was considered to be similar to that seen with commonly used agents in RA. GI perforation and demyelination adverse events were considered in light of their relative rarity, and the risks of these were not felt to outweigh the potential benefits observed with the product. The main area under discussion was the potential risk conferred by the elevation in LDL levels. Some members expressed great concern while other members were reassured by the lack of a signal for clinical cardiovascular events and by the potentially beneficial anti-inflammatory effects of tocilizumab on cardiovascular risk. The committee voted 10-to-1 in favor of approval.

Taking into account the AAC discussion, regulatory review of the BLA was completed and on January 08, 2010 a regulatory action to approve tocilizumab was taken. The Approval Letter outlined requirements specific to the tocilizumab program based on the review of the available safety data. These requirements include:

1. Risk Evaluation and Mitigation Strategies (REMS) under to ensure that the benefits of the drug outweigh the risks. The REMS consists of a Medication Guide, Communication Plan, and a timetable for submission of assessments of the REMS.

2. Post-marketing requirements (PMR):

- Pregnancy registry to evaluate pregnancy outcomes for women exposed to Actemra (tocilizumab) during pregnancy. Utilize the established Organization of Teratology Information Specialists (OTIS) pregnancy registry to evaluate pregnancy outcomes. The timetable to conduct this study is as follows:
 - Final Protocol Submission: July 30, 2010
 - Study Completion Date: December 31, 2016
 - Final Report Submission: December 31, 2017
- Long-term, observational study of patients who continue to be treated with tocilizumab in the open-label part of the treatment trials WA18695 and WA18696 to evaluate long-term serious risks of Actemra and to accrue

safety data on at least 1000-1500 patients treated for 5 years. The timeline to conduct this study is as follows:

- Final Protocol Submission: December 17, 2009
- Study Completion Date: June 30, 2013
- Final Report Submission: June 30, 2014
- A randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with tocilizumab, e.g., stroke, non-fatal MI, cardiovascular death. The timeline to conduct this study is as follows:
 - Final Protocol Submission: July 30, 2010
 - Study Completion Date: February 28, 2018
 - Final Report Submission: February 28, 2019
- A randomized trial to study the effects of tocilizumab on therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated. The timeline to conduct this study is as follows:
 - Final Protocol Submission: April 30, 2010
 - Study Completion Date: October 31, 2013
 - Final Report Submission: November 30, 2012

At the time of the original approval, the PREA requirement was to study tocilizumab in pJIA in children at least 2 years of age.

- Assessment of pharmacokinetic (PK/PD) parameters and dosing, efficacy, safety, tolerance and immunogenicity in the pediatric population ages ≥ 2 years to < 17 years with polyarticular JIA.
 - Protocol Submission: October 16, 2009
 - Final Report Submission: March 31, 2014

The pediatric study requirement for ages 0 to < 2 years for pJIA was waived as necessary studies are impossible or highly impracticable.

Subsequent to the approval of the original BLA, the applicant has submitted several supplements among which the following major safety and efficacy supplements:

- Efficacy supplement #s 7, 10, and 11, which served as the basis for approval in January 2011 of additional claims of:
 - Inhibition of radiographic progression of structural damage.
 - Improvements of physical function, and
 - Major clinical response (ACR70 response sustained for ≥ 6 months).
- Efficacy supplement #22, which served as the basis for expanding the indication to the treatment of active Systemic Juvenile Idiopathic Arthritis in patients 2 years of age and older. At the time of the approval of the supplement, April 5, 2011, the PREA requirement was to perform a PK study in children less than 2 years of age with sJIA.

- Safety supplement #49, which served as the basis for expanding the indication to adult patients with RA who have had inadequate response to one or more DMARDs as of October 2012

2.6 Other Relevant Background Information

Roche's co-development partner, Chugai Pharmaceutical Co. Ltd., has received approval in Japan in April 2005 for the use of tocilizumab in the treatment of multicentric Castleman's Disease. In April 2008, tocilizumab was approved in Japan for the treatment of adult RA, systemic juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic arthritis (pJIA).

Tocilizumab has not been withdrawn from any market or had a licensing application suspended in any country as of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The supplemental BLA submission was in electronic common technical document (eCTD) format and was adequately organized. The coding dictionary used for mapping investigator verbatim terms to preferred terms was provided upon our request following the Filing meeting.

The Sponsor reported that at a single site in Spain (CRTN #165246), a critical audit finding of non-compliance with GCP was identified as follows:

- For 19 out of a total of 67 study visits across the 6 active subjects, the joint assessments were not performed in an independent, blinded manner, as required by the protocol. Instead, these assessments were performed by the treating physicians. Consequently, the integrity of the primary efficacy data from this site may have been compromised due to breaching the requirement for blinded, independent joint assessments. The following corrective and preventive actions were taken: each such occurrence at this site was recorded as a protocol violation. The site was retrained on the independent joint assessor procedures and a back-up blinded joint assessor was identified by the site. It was also verified that a similar situation had not happened at any other sites in the study.
- At the other investigator sites audited, no critical audit findings were observed. Appropriate corrective and preventive actions were undertaken for all audit findings.

This observation indicated overall minor and sporadic regulatory deficiencies. Further, the applicant appears to have taken appropriate preventive and corrective actions in response to the audit findings. Based on these considerations, it is the reviewer's

conclusion that study WA19977 appears to have been conducted adequately and the nature of the deficiencies is unlikely to significantly impact data integrity and reliability. Therefore, no OSI inspection was requested for the current supplement.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in the supplemental BLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 11,972 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP). At one site in Spain (CRTN #165246) a non-compliance with GCP practices was identified as described in section 3.1 Submission Quality and Integrity above.

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 (v.10/09) certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No significant efficacy/safety issues have been identified by the other review disciplines.

4.1 Chemistry Manufacturing and Controls

No new CMC data were submitted with this supplement for review.

4.2 Clinical Microbiology

No new clinical microbiology data were submitted with this supplement for review.

4.3 Preclinical Pharmacology/Toxicology

No new pre-clinical data were submitted in this supplement for review.

4.4 Clinical Pharmacology

A full review of clinical pharmacology aspects of this sBLA was conducted by Dr. Liang Zhao and Dr. Atul Bhattaram. The reader is referred to Clinical Pharmacology team review for comprehensive details.

The clinical pharmacology program included PK and PD data and PK-PD relationships from the following studies MRA318JO and MRA319JP.

4.4.1 Mechanism of Action

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. IL-6 has been implicated in the pathogenesis of diseases including other inflammatory diseases, osteoporosis and neoplasia.

Tocilizumab selectively binds to soluble and membrane-bound human IL-6R, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6. The data obtained from *in vitro* assays demonstrate that tocilizumab has essentially no or minimal complement dependent cytotoxicity (CDC) activity, and little or no significant antibody dependent cellular cytotoxicity (ADCC) activity.

4.4.2 Pharmacodynamics

No new data on the mechanism of action were submitted with the current supplement for review.

4.4.3 Pharmacokinetics

Pharmacokinetic (PK) parameters were collected in study WA19977 using population PK. The population pharmacokinetic model estimated secondary exposure parameters (C_{max}, C_{min} and AUC_{4wks}) and the observed pharmacokinetic parameters (C_{wk16} and C_{trough}) in both Part I and Part II of the study were compared by treatment groups. The results confirmed that the 10 mg/kg dose in patients weighing <30 kg provided more comparable exposure to that following the 8 mg/kg dose in patients weighing ≥30 kg than for the 8 mg/kg dose in patients weighing < 30 kg.

Pharmacodynamic data (CRP, ESR, IL-6 and sIL-6) analyses showed that the 10 mg/kg dose in pJIA patients weighing < 30 kg and 8 mg/kg dose in pJIA patients weighing ≥30 kg achieved comparable pharmacodynamic responses.

4.4.4. Dose-Selection Rationale

For detailed review and discussion on sponsor's dose selection rationale, the reader is referred to the clinical pharmacology and pharmacometrics review by Dr. Liang Zhao and Dr. Atul Bhattaram.

The sponsor selected the tocilizumab doses for the confirmatory study WA19977 based on modeling and PK data from study MRA318/319JP both of which employed a single dosing regimen of 8 mg/kg every 4 week to all 19 enrolled patients.

The sponsor observed that in study MRA318JP, the clinical responses, as measured by JIA ACR30/50/70 responder rates were numerically higher among older patients (≥ 12 years) with a higher body weight and a higher body mass index. This difference in JIA ACR response rate was associated with a trend toward lower systemic exposure (AUC_{4wk}) in TCZ subjects with lower body weight, particularly below a body weight of 33 kg as shown in Table 3 and Figure 1 (dotted line). After 12 weeks of treatment with TCZ 8 mg/kg every 4 weeks, 89% of patients weighing < 33 kg vs 100% of the patients weighing ≥ 33 kg achieved a JIA ACR50 response; and 44% of patients weighing < 33 kg vs. 70% of patients weighing ≥ 33 kg achieved JIA ACR70 response. Based on these observations, the sponsor performed a PK model which predicted AUC_{4wk} for body weight < 30 kg with a 10 mg/kg dose as shown in Figure 1 (solid line).

Modeling and simulation results indicated that to achieve comparable exposure across the range of body weights, the TCZ dose should be 8 mg/kg for patients with body weight ≥ 30 kg and the TCZ dose should be 10 mg/kg for patients with body weight < 30 kg.

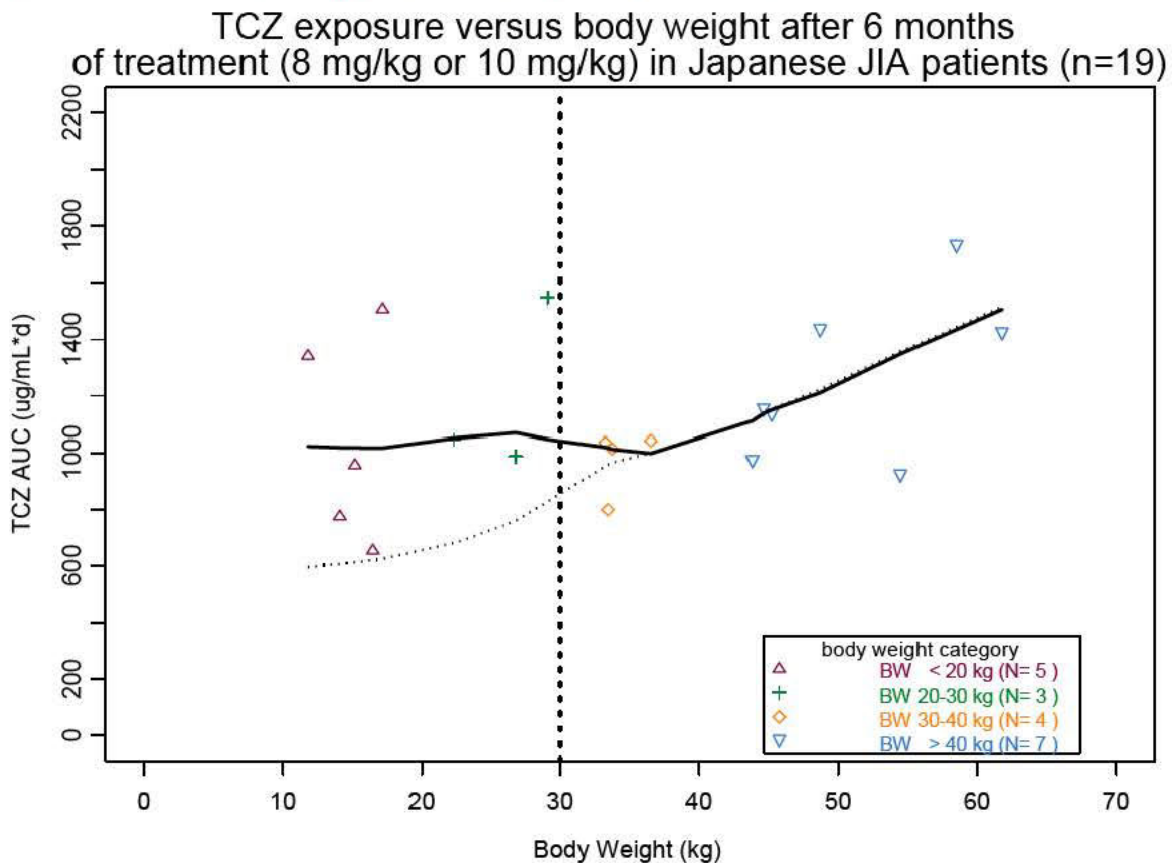
These observations and PK modeling predictions provided the rationale for exploring an increased dose of TCZ in patients with lower body weights in the pivotal study. Therefore, the study was designed to assess efficacy and safety for both 8 mg/kg and 10 mg/kg doses in patients with body weight less than 30 kg in a randomized manner as described in detail in section 9.4.1.1 Study WA19977: Design.

Table 3. JIA ACR Response Rates at Week 12, Study MRA318JP

JIA ACR Responses at Week 12, Study MRA318JP		
	Improved, n	Rate
BW ≥33 kg (N=10)		
ACR30	10	100%
ACR50	10	100%
ACR70	7	70%
BW <33 kg (N=9)		
ACR30	8	89%
ACR50	8	89%
ACR70	4	44%

Source: CSR MRA318JP

Figure 1. Tocilizumab Exposure by Body Weight, Study MRA318JP



Source: Summary of Clinical Pharmacology, Figure 26

5 Sources of Clinical Data

The BLA 125276/64 was submitted on June 28, 2012 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report including protocols, statistical analysis plan, and all referenced literature can be found in the EDR using the following path:

\\cbsap58\m\CTD_Submissions\STN125276\125276.enx

5.1 Tables of Studies/Clinical Trials

The clinical efficacy and safety data to support the current BLA supplements are derived from the pivotal study WA19977 and additional the supportive Japanese studies MRA318 JP and MRA319JP. Key design features of these studies are summarized in Table 4 below.

Table 4. Key Design Features of Studies WA19977, MRA318JP and MRA319JP

Study	Design	Patients
Pivotal phase III trial to evaluate efficacy and safety of TCZ in patients with pJIA:		
WA19977	Two-year study in three parts: <u>Part I</u> : 16-week open-label TCZ therapy: BW ≥ 30 kg: 8 mg/kg TCZ IV q4w BW < 30 kg: 8 or 10 mg/kg TCZ IV q4w <u>Part II</u> : 24-week double-blind, placebo-controlled, randomized withdrawal period in patients achieving JIA ACR30 response at week 16 of Part I; same TCZ dose as in Part I or placebo <u>Part III</u> : 64-week open-label extension (ongoing)	Patients with pJIA for at least six months and with at least five active joints; age at screening was 2-17 years. Treated in <u>Part I</u> : N = 188 (8 mg/kg TCZ: n = 153; 10 mg/kg TCZ: n = 35) Treated in <u>Part II</u> : N = 163 (8 mg/kg TCZ: n = 66; 10 mg/kg TCZ: n = 16; placebo: n = 81)
Supportive trials:		
MRA318JP	12-week open-label, single-arm study; TCZ dose 8 mg/kg IV q4w	Japanese patients with pJIA with at least five active joints; age at baseline 3-19 years; N = 19
MRA319JP	Long-term extension of MRA318JP; total TCZ 8 mg/kg IV q4w treatment duration 0.35–3.53 years	Patients who completed MRA318JP: N = 19
ML21939 (JPMS)	6-month observational cohort study in Japan	pJIA patients: N = 179

Source: Clinical Overview

5.2 Review Strategy

Study WA19977 was used as the primary source of clinical efficacy and safety data to support this submission. Primary evidence of efficacy was based on superiority of continued TCZ over placebo withdrawal in the rate of ACR JIA30 flares between Week 16 and Week 40, as assessed by pre-specified analyses and corroborated by secondary and sensitivity analyses. The study was conducted under a special protocol agreement granted in May of 2009. The same study provided also the primary evidence of safety with a clinical data cut-off date of November 4, 2011 and a subsequent 120-day safety follow up cut-off date of May 3, 2012.

Additional efficacy data were used from the supportive studies in the Chugai Japanese program studies to corroborate the clinical efficacy findings from the pivotal study. Safety data from these studies and from the Japanese Post-Marketing Surveillance (JPMS) study ML21939 were evaluated with respect to deaths, serious adverse events, and other adverse events of interest.

To further assess the safety in pJIA program, relative to safety in sJIA and adult RA populations, data from the respective updated development programs was compared descriptively.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study WA19977

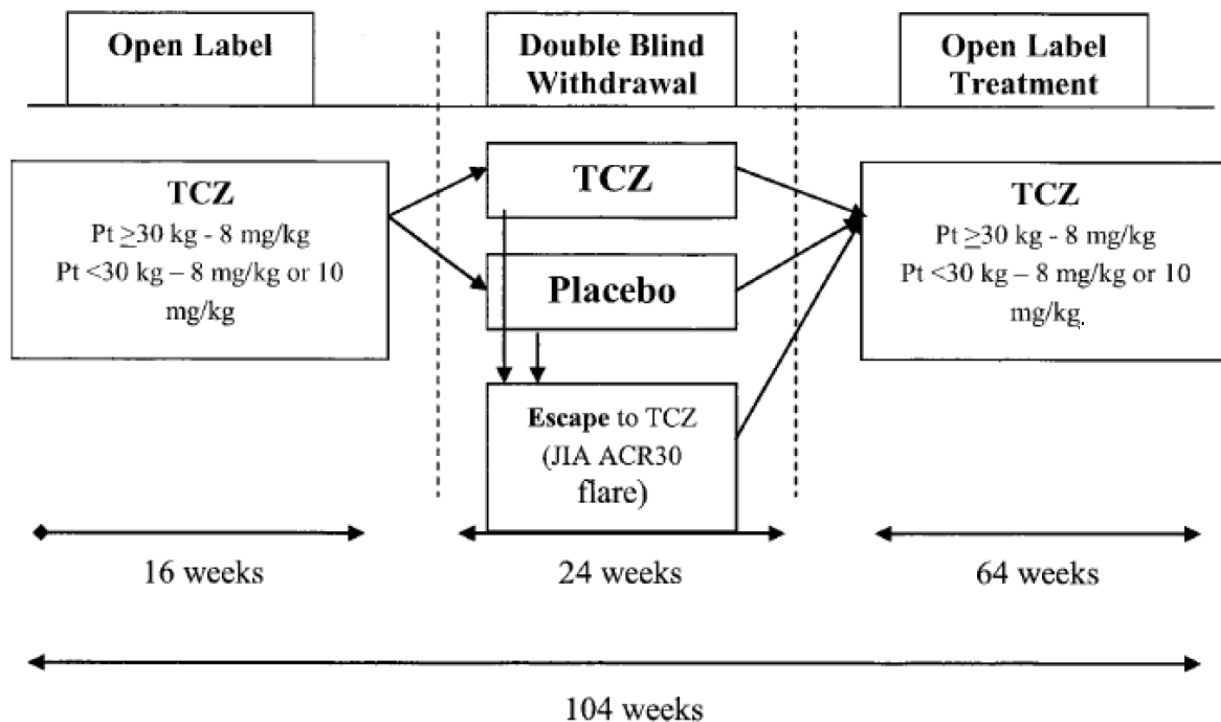
This is an ongoing three-part Phase 3 study to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in patients with active pJIA. The study design is summarized in Figure 2. The targeted population consisted of patients who had shown an inadequate response to MTX or were intolerant to MTX. However, concomitant MTX was permitted during the study.

- Part I (complete) was a 16-week open-label TCZ treatment lead-in period:
 - All patients weighing at least 30 kg received 8 mg/kg TCZ IV every 4 weeks (q4w).
 - Patients weighing less than 30 kg were randomized in a 1:1 ratio to either 8 mg/kg or 10 mg/kg TCZ q4w.
 - Efficacy was assessed using the JIA American College of Rheumatology (ACR) response measure. Patients who achieved at least a 30% improvement (i.e., a JIA ACR30 response) at week 16 compared to baseline were eligible to enter Part II.

Data from this period of the study provided short-term (16 weeks) evidence of relative safety and efficacy between the two studied dosing regimens 8 mg/kg (n=34) or 10 mg/kg (n=35) TCZ q4w in patients weighing less than 30 kg.

- Part II (complete) was a 24-week randomized, double-blind, placebo-controlled withdrawal period in which patients were randomized in a 1:1 ratio to treatment with TCZ at the same dose level as in Part I or to placebo. Randomization was stratified by concomitant MTX use and concomitant oral corticosteroid use. Patients who developed a JIA ACR30 flare relative to week 16 qualified for escape therapy with TCZ at the same dose as in Part I. The data from this period of the study provided the primary evidence of efficacy.
- Part III (ongoing) is a 64-week open-label period beginning at week 40 (or once a patient entered escape therapy with TCZ) to examine the long-term use of TCZ on safety and efficacy. In patients originally randomized to the TCZ 10 mg/kg dose, the investigator had the option to reduce the TCZ dose level to 8 mg/kg if the patient's body weight had increased to ≥ 30 kg and was at least 5 kg above the baseline weight for three consecutive visits. Part III is ongoing. The last patient's last visit is expected for January 2013.

Figure 2. Study Schema for Study WA19977



Source: Clinical Protocol WA19977

The protocol and the statistical analysis plan specified the following analysis patient populations:

- Intent-to-Treat (ITT): All patients who were randomized into the lead-in phase and subsequently received at least 1 dose of TCZ.
 - In addition an ITT population was defined for the Part I patients only (ie, those patients who participated in Part I), which was effectively the all ITT population.
 - An ITT Part II population was also defined, this was the subset of patients from the ITT Part I who were subsequently randomized at Week 16 (beginning of Part II) to either placebo or TCZ. ITT treatment group allocation was as randomized at baseline and Week 16.
- Safety Population included all patients who were randomized into the lead-in phase study Part I and subsequently received at least one i.v. infusion of TCZ and were also required to have had at least one post-Baseline assessment or event concerning safety (i.e. AEs, concomitant medications, laboratory data and vital signs). Despite the pre-defined limitation for inclusion in the safety population, all 188 enrolled patients had a post-Baseline assessment and were included in the safety analyses.
- All Exposure Population included all data in the study database up to and including the 04 November 2011 (updated with data from 120-day safety update with clinical data cut-off date of May 03, 2012). To account for the different exposure the sponsor has also presented the data adjusted for exposure as events per 100 patient-years. Of note for the “All exposure” population, the data includes the total tocilizumab exposure but does not discriminate between patients who have received continuous tocilizumab throughout the study and those who received placebo and then re-initiated tocilizumab during randomized withdrawal in Part II. Therefore, the pooled data from this patient population should be interpreted with caution.
- Per-Protocol (PP) population excluded patients that had events that were considered as potentially influencing the efficacy analysis.
- Pharmacokinetic (PK) Population:
 - Study Part I (PK-1) population included all patients who had a non-missing area under the curve (AUC)[4 weeks], minimum serum concentration (Cmin) and maximum serum concentration (Cmax) to Week 16.
 - Study Part II (PK-2) population included only patients that were randomized to TCZ treatment at Week 16 and who had a non-missing AUC[4 weeks], Cmin and Cmax to Week 40.

Detailed description of study WA19977 is provided in section 9.4 Individual Study Reports below.

5.3.2 Supportive Japanese Studies

5.3.2.1 Study MRA318JP

This was an open-label study conducted at five sites in Japan between November 2004 and July 2005. Patients were given three TCZ infusions of 8 mg/kg at 4-week intervals. The last observations were made at the week 12 visit, 4 weeks after the last infusion. The dose regimen and duration of treatment were based on the TCZ dosage regimen for RA in adults. In contrast to study WA19977, concomitant treatment with any DMARDs, including MTX, was not permitted. The study enrolled patients 2 to 19 years of age who had been under 16 years of age at disease onset. Patients had to have a diagnosis of RF-positive or RF-negative polyarticular JIA or oligoarticular JIA according to the ILAR criteria. The primary efficacy analysis was JIA ACR30 response on the last observation day.

Detailed description of study MRA318JP is provided in section 9.4 Individual Study Reports below.

5.3.2.2 Study MRA319JP

This was the long-term extension of study MRA318JP. The primary objective was to investigate the safety, efficacy, and pharmacokinetics of long-term treatment with TCZ for pJIA. Patients continued to receive open-label TCZ at a dose of 8 mg/kg q4w for at least one year after the first infusion in MRA318JP.

Detailed description of study MRA319JP is provided in section 9.4 Individual Study Reports below.

6 Review of Efficacy

6.1 Indication

The Sponsor proposes the following supplemental indication:

“Actemra is indicated for the treatment of active pJIA in patients 2 years of age and older.”

6.1.1 Methods

Clinical efficacy data to provide evidence for regulatory approval of the proposed indication was derived from a single definitive study, WA19977, conducted under

special protocol agreement. The study has enrolled pediatric patients, ages 2 through 17 years old with moderately-to-severely active pJIA who have had inadequate clinical response or intolerance to MTX, which is a common scenario in clinical practice. The study design allowed but did not require a continuation of the background MTX at stable doses and specified provisions for withdrawal for safety.

The applicant has pre-specified an analysis plan to assess the primary endpoint at Week 40 compared to Week 16 which is the double-blind withdrawal period of the study by comparing the pooled data from tocilizumab-treated patients (two dosing regimens,) to placebo.

Key secondary endpoints, pre-specified in the statistical analysis plan, assess clinical responses from a different time interval as measured by change from baseline to Week 40. This interval includes the open-label lead in period (Part I) and double-blind withdrawal period (Part II), therefore some patients have received tocilizumab for shorter duration if they were randomized to placebo in Part II.

Additional efficacy analyses compare the clinical responses among the three dosing regimens during the open-label lead in period (Part I). These data were utilized in the assessment of the relative risk-benefit for dose selection and recommendations as discussed in section Analysis of Clinical Information Relevant to Dosing Recommendations.

Supportive efficacy data were also derived from the clinical study reports of studies MRA318/319JP.

6.1.2 Demographics

Study WA19977

A total of 188 patients were enrolled and treated in study WA19977. The study was conducted at 58 sites; 4 sites in Argentina, 2 sites in Australia, 2 sites in Belgium, 4 sites in Brazil, 4 sites in Canada, 4 sites in France, 4 sites in Germany, 4 sites in Italy, 4 sites in Mexico, 3 sites in Peru, 5 sites in Poland, 6 sites in Russian Federation, 2 sites in Spain, 3 sites in the United Kingdom, and 7 sites in the United States (US). While this was a global program, the study had enrolled patients from several North American sites, including US, which allows for a general comparison across regions to determine the applicability of the findings to the US pJIA population.

The overall demographic and disease characteristics were fairly well balanced among the treatment groups as summarized in Table 5. The study population consists of more females, white and of non-Hispanic ethnicity. As expected, the group of patients heavier than 30 kg consists of older patients (mean age 13 vs. about 7 years) with longer disease duration (mean of 4.7 vs. 3.5 years) and more prevalent prior biologic exposure

(39% vs. about 20% of patients) as compared with the patients with body weight of 30 kg or lower. The overall disease activity however, as measured by the numbers of joints with active arthritis and limitation of motion, patient/parent and physician global assessments, and CHAQ-DI scores, is comparable among all treatment groups.

Table 5. Baseline Demographic and Disease Characteristics, Study WA19977

Baseline Demographic and Disease Characteristics, Study WA19977				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Randomized and treated	35	34	119	188
Age (years), mean (SD)	6.9 (3.0)	7.6 (2.7)	13.1 (2.8)	11.0 (4.0)
Females, n (%)	30 (86)	24 (71)	90 (76)	144 (77)
White Race, n (%)	28 (80)	28 (82)	94 (79)	150 (80)
Non-Hispanic ethnicity, n (%)	22 (63)	23 (68)	80 (67)	125 (66)
Weight (kg), mean (SD)	20.7 (6)	22.4 (5)	50.0 (13)	39.6 (17)
Height (cm), mean (SD)	117 (15)	120 (14)	154 (14)	141 (22)
Body surface area (m ²), mean (SD)	0.8 (0.2)	0.9 (0.2)	1.5 (0.2)	1.2 (0.4)
Disease duration (years), mean (SD)	3.4 (2.4)	3.5 (2.6)	4.7 (4.2)	4.2 (3.4)
Prior DMARDs use, n (%)	21 (60)	26 (76)	87 (73)	134 (71)
Prior biologics use, n (%)	8 (23)	6 (18)	47 (39)	61 (32)
Number of Joints with Active Arthritis, mean (SD)	24 (18)	21 (14)	19 (13)	20 (14)
Number of Joints with LOM, mean (SD)	23 (19)	17 (13)	16 (13)	18 (14)
Patient/Parent Global Assessment VAS, mean (SD)	52 (27)	59 (26)	52 (24)	53 (25)
Physician Global Assessment VAS, mean (SD)	65 (21)	65 (19)	59 (21)	61 (21)
CHAQ-DI Score, mean (SD)	1.7 (0.7)	1.8 (0.7)	1.2 (0.7)	1.4 (0.7)
ESR, mean (SD)	35 (24)	37 (23)	34 (27)	35 (26)
Concurrent Methotrexate Use, n (%)	29 (83)	30 (88)	89 (75)	148 (79)
Median Dose mg/m ² /week	14	14	11	12
Corticosteroid Use, n (%)	15 (43)	18 (53)	54 (45)	87 (46)
Average Dose (mg/kg/day), mean	0.15	0.15	0.12	0.13

Source: CSR WA19977, adapted from Table 7, BW-body weight, SD-standard deviation.

Concomitant use of DMARDs other than methotrexate and biologics was not permitted in the study. As shown in Table 5, methotrexate was used concomitantly by the majority of the patients (about 80%) and was similar across treatment groups. Systemic corticosteroids were used by about one half patients with similar proportions of users across treatment groups. These observations indicate comparable management of disease activity and are generally representative of clinical practice.

Study MRA318JP:

A total of 19 patients were enrolled and treated in five centers in the Japanese study MRA318JP. Baseline demographic and disease characteristics are summarized in Table 6. Similarly to study WA19977, the enrolled patients were predominantly females of comparable age (mean 11 years), with slightly longer disease duration (mean 5.3 years). The overall disease activity is also generally comparable between the two studies as measured by mean patient/parent and physician global assessment and CHAQ-DI scores, despite the lower mean count of joints with active arthritis and limited range of motion.

Table 6. Baseline Demographic and Disease Characteristics, Study MRA318JP

Baseline Demographic and Disease Characteristics, Study MRA318JP	
Randomized and treated, n	19
Age (years), mean (SD)	11.6 (5)
Females, n (%)	15 (79)
Weight (kg), mean (SD)	34 (16)
Height (cm), mean (SD)	133 (24)
Body surface area (m ²), mean (SD)	1.1 (0.4)
Disease duration (years), mean (SD)	5.3 (5)
Prior DMARD, including biologic use, n (%)	19 (100)
Number of Joints with Active Arthritis, mean (SD)	14 (10)
Number of Joints with LOM, mean (SD)	9 (7)
ESR, mean (SD)	47 (20)
CRP, mean (SD)	2.7 (2)
Patient/Parent Global Assessment VAS, mean (SD)	59 (26)
Physician Global Assessment VAS, mean (SD)	64 (21)
CHAQ-DI Score, mean (SD) ESR, mean (SD)	1.34 (0.9)
Corticosteroid Use, n (%)	15 (79)
Average Dose (mg/kg/day) (SD)	0.14 (0.1)

Source: CSR MRA318JP, Adapted from table 11.2-1

6.1.3 Subject Disposition

During the open-label lead-in period (Part I, weeks 0-16), a total of 22 patients withdrew from the study as summarized in Table 7. The majority of these patients (15/22) withdrew because they failed to achieve the pre-defined JIA ACR30 response. Among these, the highest proportion 18%, 6/34) was in the patients with body weight <30 kg treated with the 8 mg/kg (lower dose) of tocilizumab as compared with the other two groups. These observations are consistent with the findings of study MRA318JP and are further discussed in the context of the dose-selection rationale in section 4.4

Clinical Pharmacology. Of the remaining seven patients, four withdrew because of adverse events (serum sickness-like reaction, sclerosing cholangitis, and benign

intracranial hypertension, pneumonia), three refused treatment/withdrew consent, and one was lost to follow up. The overall rate of completers of Part I, i.e. patients who have achieved the pre-specified JIA ACR30 response rate was 88%, which is higher than assumed for the sample size calculation and recruitment target as discussed in section 9.4.1.1 Study WA19977: Design.

Table 7. Patient Disposition, Part I (Week 16), in Study WA19977

Patient Disposition, Part I (Week 16), in Study WA19977				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Randomized and treated	35	34	119	188
Completed Part I, n (%)	31 (89)	24 (71)	111 (93)	166 (88)
Discontinuations, n (%)	4 (11)	10 (29)	8 (7)	22 (12)
<i>Lack of efficacy (JIA ACR30 response)</i>	4 (11)	6 (18)	5 (4)	15 (8)
<i>Adverse events</i>	0	1	2	3
<i>Withdrew consent</i>	0	2	1	3
<i>Lost to follow up</i>	0	1	0	1

Source: CSR WA19977, adapted from Figure 1 and Tables stex11_1, slae01_wd_ae
 BW=body weight

Out of the total of 188 patients, 166 patients were randomized to treatment in Part II, with 84 patients randomized to placebo and 82 to TCZ. Three patients randomized to placebo did not receive an infusion in this study period and were not included in the ITT population for Part II. Of the 163 patients who received treatment in Part II, 60 had JIA ACR30 flares and qualified for escape treatment until completion of Part II and entry into Part III, and 100 completed the 24 weeks of double-blind placebo-controlled treatment (CSR WA19977 Figure 2).

The patient disposition during the randomized withdrawal period (Part II, weeks 17-40) is summarized in Table 8. Two patients withdrew due to AEs (one in the 10 mg/kg group, body weight <30 kg, who developed abnormal bilirubin elevation, one in the placebo group, body weight ≥30 kg who developed gastroenteritis) and three patients withdrew consent. The overall retention rate was high and comparable across the treatment groups allowing for generally meaningful comparisons.

Table 8. Patient Disposition, Part II (Week 40), in Study WA19977

Patient Disposition, Part II (Week 40), in Study WA19977						
	TCZ (N=82)			Placebo (N=84)		
	BW <30 kg		BW ≥30 kg	BW <30 kg		BW ≥30 kg
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg
Randomized and treated, ITT	16	11	55	15	13	53**
Completed Part II, n (%)	15 (94)	11 (100)	52 (95)	15 (100)	13 (100)	52 (98)
Discontinuations	1	0	3	0	0	1
<i>Adverse events</i>	1	0	0	0	0	1
<i>Withdrew consent</i>	0	0	3*	0	0	0

Source: CSR WA19977, adapted from Figure 2 and Table stex11_2, slae01_wd_ae
 BW-body weight
 * Patient 2583 missed the Week 16 infusion, completed Week 18 and then withdrew at the next visit; Patients 2122 and 2682 withdrew while receiving Part II escape medication.
 ** A total of 56 patients were randomized but three patients received no infusion in Part II and were not included in the ITT population (table stec11_rnd_a_2)

Part III is ongoing and the patients' disposition data are summarized in Table 9 as of the 120-day safety update with a clinical data cut-off date of May 03, 2012. During this period, the protocol specified that patients with baseline weight <30 kg treated with 10 mg/kg tocilizumab, who have gained at least 5 kg and reached a weight of ≥30 kg were allowed to have their dose modified to 8 mg/kg. A total of 12 patients met these criteria and had their dose reduced to 8 mg/kg. One patient with body weight <30 kg, discontinued due to SAE coded as scleroderma after having received 21 infusions of tocilizumab 10 mg/kg dose. A summary of patient disposition in the all exposure population is presented in Table 9 and indicates findings consistent with the observations from the Parts I and II of the study.

Table 9. Patient Disposition, All Exposure Population, in Study WA19977 As of May 03, 2012

Patient Disposition, All Exposure Population, in Study WA19977, As of May 03, 2012					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
Exposure, patient-years	28	19	38	170	255
Discontinuations, n (rate per 100 PYs)	6 (21)	0	11 (29)	14 (8)	30 (12)
<i>Lack of efficacy (JIA ACR30 response)</i>	4	0	7	7	18
<i>Adverse events</i>	2	0	1	3	6
<i>Withdrew consent</i>	0	0	2	4	6
<i>Lost to follow up</i>	0	0	1	0	1

Source: CSR WA19977 and 120-Day Safety Update, adapted from Figure 2 and Tables stex11_1, slae01_wd_ae
 BW-body weight; PY-patient-year
 * In Part III only, 12 patients had their TCZ dose decreased to 8 mg/kg as their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits

There were no deaths in study WA19977. Further, the sponsor reported no major protocol violations for which patients were excluded from the analyses.

Supportive Japanese studies MRA318/319JP

No patients withdrew from study MRA 318JP. Of the 19 patients rolled over from study MRA318JP into study MRA319JP, four discontinued: one due to an AE (myasthenia gravis), one due to development of anti-TCZ antibodies before the 4th infusion without associated AEs or loss of efficacy, and two due to insufficient therapeutic response.

6.1.4 Analysis of Primary Endpoint(s)

Endpoints:

The key efficacy measure in this program was based on Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology (ACR) composite endpoint. The JIA core set consists of the following parameters:

- Parent/patient global assessment of overall well-being
- Physician global assessment of disease activity
- Number of joints with active arthritis
- Number of joints with limitation of movement
- Erythrocyte sedimentation rate (ESR)

The primary efficacy measure was JIA ACR30 flare rate defined as 3 of any 6 core outcome variables worsening by at least 30%, with no more than 1 of the remaining variables improved by more than 30% since the evaluation at Week 16. If either number of joints with active arthritis or number of joints with limitation of motion was used in the calculation of flare for a study visit in a patient, then a minimum worsening of at least two active joints or two joints with limitation of motion had to be present. If either the Physician Global Assessment or the Parent/patient Global Assessment were used in the calculation of flare for a study visit in a patient, then a minimum worsening of at least 20 units on a scale from 0 to 100 had to be present. If a condition was not satisfied then that particular JIA ACR core component was not considered as worsening.

The primary endpoint in study WA19977 was defined as the proportion of patients who develop a Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology (ACR) 30 flare (relative to Week 16) in study Part II (i.e. by Week 40). The ITT population was used for the primary endpoint assessment as pre-specified.

Primary Analysis Results:

The study met its primary efficacy endpoint at week 40 with 48.1% of patients receiving placebo experiencing a JIA ACR30 flare between weeks 16 and 40 compared to 25.6% of patients receiving TCZ (p=0.0024) as summarized in Table 10 below. This analysis adjusted for the randomization stratification (background use of MTX and oral corticosteroids) as pre-specified and agreed upon with sponsor at the time of the special protocol assessment. The results from the primary analysis demonstrate a statistically significant and clinically meaningful difference between the two groups providing evidence of efficacy of tocilizumab in treating patients with active pJIA.

Table 10. Primary Endpoint: Cochran-Mantel-Haenszel Analysis of the Proportion with JIA ACR30 Flare at Week 40 Relative to Week 16 (ITT Population)

Primary Analysis: Proportion with JIA ACR30 Flare at Week 40 Relative to Week 16 (ITT Population)		
	All Placebo	All TCZ
N	81	82
Flared, n (%)	39 (48%)	21 (26%)
95% CI	0.37, 0.59	0.16, 0.35
Weighted difference vs. PBO	-	-0.21
p-value		0.0024
Source: CSR WA19977, adapted from Table etepcmh03_ja3fw_v1_rx2_it2_p2		

Sensitivity Analyses:

To support the findings of the primary analyses, the sponsor has conducted the following sensitivity analyses of the primary outcome measure:

- Cochran-Mantel-Haenszel Analysis of the proportion of Patients with JIA ACR30 flare rates accounting for patients who withdrew for reasons other than disease flare, including all withdrawals during Part II. The results from this analysis are consistent with the primary analysis as summarized in Table 11.

Table 11. Sensitivity Analysis: Cochran-Mantel-Haenszel Analysis of the Proportion with JIA ACR30 Flare and Other Withdrawals at Week 40 Relative to Week 16 (ITT Population)

Sensitivity Analysis: Proportion with JIA ACR30 Flare and Other Withdrawals at Week 40 Relative to Week 16 (ITT Population)		
	All Placebo	All TCZ
N	81	82
Flared, n (%)	34 (42%)	14 (17%)
95% CI	0.3, 0.5	0.1, 0.3
Weighted difference vs. PBO	-	-0.24
p-value		0.0003

Source: CSR WA19977, adapted from Table etepcmh03_ja3f1_v1_rx2_it2_p2

- A logistic regression analysis of the proportion of patients with JIA ACR30 flare in the ITT population during Part II. The results from this analysis as summarized in Table 12 are also supportive of the primary analysis.

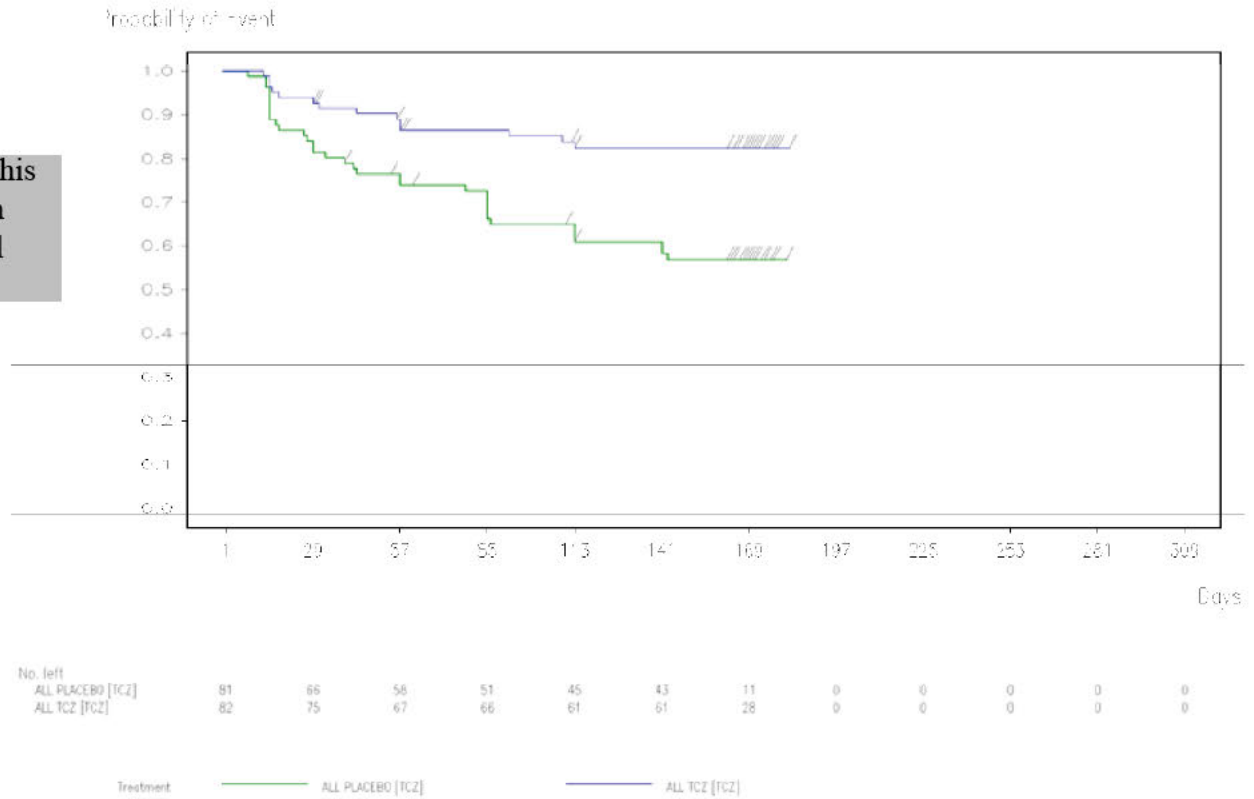
Table 12. Sensitivity Analysis: Logistic Regression of the Proportion with JIA ACR30 Flare at Week 40 Relative to Week 16 (ITT Population)

Sensitivity Analysis: Logistic Regression of the Proportion with JIA ACR30 Flare at Week 40 Relative to Week 16 (ITT Population)			
	Odds Ratio	95% CI	p-value
Treatment comparison (reference All Placebo)	0.35	0.2, 0.7	0.0035

Source: CSR WA19977, adapted from Table eteplog01_ja3fw_v1_rx2_it2_p2

- Kaplan-Meier analyses of time to JIA ACR30 flare also demonstrated that more patients randomized to placebo flared compared with patients who continued to receive tocilizumab during Part II of the study as shown in Figure 3. The separation between the two groups was evident from day 28.

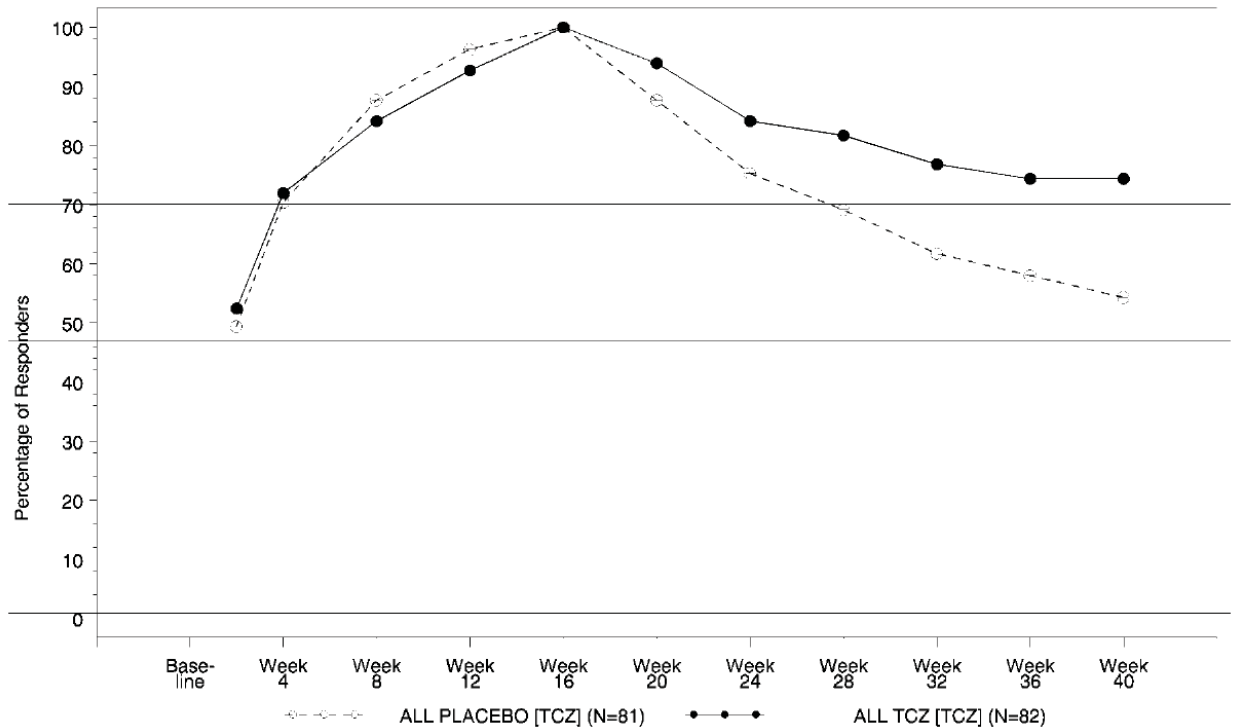
Figure 3. Kaplan-Meier Plot of the Time (Days) to JIA ACR30 Flare After Randomization into Withdrawal Phase (Withdrawal Phase Study Part II, ITT Population – Study Part II)



Source: CSR WA19977, adapted from Figure 5

- Kinetics of JIA ACR responder rates over time also indicate separation between the two groups after the time of withdrawal as shown in Figure 4. These differences were paralleled by similar differences in the JIA ACR core components over time.

Figure 4. Line Plot of JIA ACR30 Response Rates by Visit (Lead-In Phase Study Part I + Withdrawal Phase Study Part II, ITT Population – Study Part II)



Source: CSR WA19977, Figure 7

In summary, the pre-specified analysis of primary efficacy endpoint, supported by the sensitivity analyses of the outcome measure, have demonstrated statistically significant and clinically meaningful efficacy of tocilizumab in pediatric patients with active polyarticular course JIA.

6.1.5 Analysis of Secondary Endpoints(s)

The presentation of the secondary endpoints in this review focuses on the secondary endpoints for which a hierarchical testing was pre-specified in order to control for Type I error as shown in Table 62. The key secondary efficacy endpoints in Part II were compared to baseline values with the caveat that all patients that rolled over to Part II were responders at Week 16 as pre-specified in the protocol and the comparison to baseline reflects the placebo-controlled treatment withdrawal during Part II of the study. From the 188 patients initially enrolled, a 166 were responders and eligible to enroll in Part II, of whom 163 were randomized and treated in Part II, decreasing the ITT population for Part II analyses. However, these numbers satisfied the statistical assumptions for sample size calculations as discussed elsewhere in this review.

Key secondary endpoints, most of which are well validated efficacy endpoints, included:

- JIA ACR30/50/70 response rates were defined as 3 of any 6 core outcome variables improved by at least 30, 50, or 70%, respectively, from the baseline assessments, with no more than 1 of the remaining variables worsened by more than 30%.
- Change from baseline to Week 40 in:
 - Number of active joints and joints with limitation in the range of motion
 - Physician’s global assessments visual analogue scale (VAS)
 - Pain VAS
 - Number of joints with limited ROM
 - Patient/parent global assessment VAS
 - ESR
- Child Health Assessment Questionnaire-Disability Index (CHAQ-DI) score
- JIA ACR90 Responder rate
- Proportion with inactive disease

Although the hierarchical sequence of significance was broken after the sixth endpoint (change from baseline to Week 40 in the pain VAS), all secondary endpoints showed consistent numerical improvement in tocilizumab-treated patients as compared with placebo withdrawals as summarized in Table 13.

Table 13. Summary of Key Secondary Endpoint Results

Summary of Key Secondary Endpoints, Study WA19977, (Week 40)			
	All Placebo	All TCZ	p-value
N	81	82	
JIA ACR30 Responder rate, n (%)	44 (54.3%)	61 (74.4%)	0.0084
JIA ACR50 Responder rate, n (%)	42 (51.9%)	60 (73.2%)	0.005
JIA ACR70 Responder rate, n (%)	34 (42.0%)	53 (64.6%)	0.0032
CFB in Number of active joints, mean	-11	-14	0.0435
CFB in Physician’s global assessments VAS, mean	-35	-45	0.0031
CFB in Pain VAS, mean	-22	-32	0.0076
CFB in Number of joints with limited ROM, mean	-8	-10	0.1229
CFB in Patient/parent global assessment VAS, mean	-25	-32	*****
CFB in ESR (mm/hr), mean	-12	-26	*****
CHAQ-DI score	-0.6	-0.8	*****
JIA ACR90 Responder rate, n (%)	19 (23.5%)	37 (45.1%)	*****
Proportion with inactive disease, n (%)	12 (14.8%)	26 (31.7%)	*****

Source: CSR WA19977, adapted from Table 9
 CFB-change from baseline; CHAQ-DI-children health assessment questionnaire-disability index; ROM-range of motion;
 VAS-visual analogue scale

JIA ACR Responses

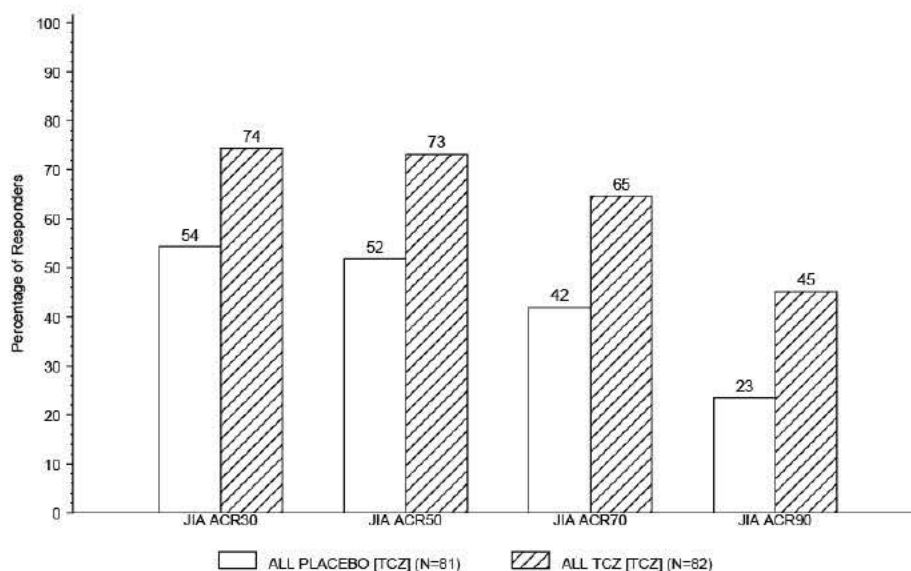
Key secondary endpoints included the proportions of patients with JIA ACR 30%, 50%, and 70% improvement compared to baseline. Overall, higher proportions of patients achieved JIA ACR 30, 50, and 70 in continuous tocilizumab-treated patients compared with patients randomized to withdrawal to placebo as shown in Table 14 and Figure 5 supporting the efficacy of tocilizumab treatment in this patient population. In addition, while the JIA ACR90 responses were not statistically significant due to adjustment for multiplicity, the trend remained consistent with the overall JIA ACR responses.

Table 14. JIA ACR30/50/70/90 Responses at Week 40, Change from Baseline, Study WA19977

JIA ACR Responses at Week 40, Change from Baseline, Study WA19977 (ITT Population Part II)			
	All placebo N=81	All tocilizumab N=82	P value
JIA ACR30, n (%)	44 (54.3%)	61 (74.4%)	0.009
JIA ACR50, n (%)	42 (51.9%)	60 (73.2%)	0.005
JIA ACR70, n (%)	34 (42.0%)	53 (64.6%)	0.003
JIA ACR90, n (%)	19 (23.5%)	37 (45.1%)	N.S.*

Source: Summary of Clinical Efficacy, adapted from Table 14
 *ACR90 responses were not statistically significant after adjusting for multiplicity as pre-specified in the protocol

Figure 5. JIA ACR30/50/70/90 Responses at Week 40, Change from Baseline, Study WA19977



Source: Summary of Clinical Efficacy, Figure 4.

JIA ACR Core Components at Week 40

JIA ACR response is derived from 6 components: the number of active joints, the number of joints with a limitation of movement, the patient/parent global assessment of global well-being VAS, the physician global assessment of disease activity VAS, the CHAQ-DI score, and the ESR.

The baseline JIA ACR core components were generally comparable between the continuous tocilizumab and placebo withdrawal patients as shown in Table 15 with small numerical imbalances observed in patient/parent and physician global assessments VAS, and CHAQ-DI. At the end of Part I, after 16 weeks of tocilizumab treatment, the patients in both groups showed comparable improvement in the JIA ACR core components with numerically lower responses in patient/parent and physician global assessments VAS in the patients to be randomized to placebo in Part II which appear proportional to the baseline differences.

Change from baseline to Week 40 indicate that patients with continuous tocilizumab exposure had numerically higher improvement compared with patients randomized to placebo during the Part II, in the number of active joints, number of joints with limitation of motion, CHAQ-DI, physician global assessments VAS, and ESR. Patient/parent global assessments VAS improved similarly between the two groups.

The overall results indicate that the improvements seen in JIA ACR response are not driven by any single component but rather by improvement in all JIA ACR core components.

Table 15. Summary of JIA ACR Core Components, Study WA19977 (ITT Population Part II)

Summary of JIA ACR Core Components, Study WA19977 (ITT Population Part II)						
	Number of active joints	Number of joints with a LOM	Patient/parent global assessment VAS	Physician global assessment of disease activity VAS	CHAQ-DI score	ESR
All Placebo Part II (N = 81)						
Baseline, mean (SD)	20 (14)	17 (14)	59 (23)	64 (19)	1.5 (0.7)	36 (26)
Week 16, mean (SD)	6 (8)	6 (8)	23 (22)	18 (15)	0.7 (0.6)	7 (9)
Week 40, mean (SD)	3 (6)	5 (9)	13 (16)	10 (11)	0.5 (0.6)	13 (9)
Week 40 CFB, mean (SD)*	- 11.5 (13)	- 8.1 (10)	- 32.4 (29)	- 38.2 (25)	- 0.7 (0.7)	- 14.0 (28)
All TCZ Part II (N = 82)						
Baseline, mean (SD)	20 (14)	17 (14)	46 (23)	58 (20)	1.2 (0.7)	32 (23)
Week 16, mean (SD)	6 (10)	8 (10)	16 (17)	14 (12)	0.5 (0.5)	7 (8)
Week 40, mean (SD)	3 (8)	4 (7)	9 (16)	6 (8)	0.3 (0.4)	5 (6)
Week 40 CFB, mean (SD)*	- 14.5 (11)	- 10.2 (9)	- 31.1 (29)	- 45.6 (21)	- 0.8 (0.7)	- 25.2 (22)

Source: WA19977 CSR, adapted from Table 15
 *Change from baseline was calculated using last observation carried forward imputation for missing values, in other rows missing values were not imputed; LOM-limitation of movement;

6.1.6 Other Endpoints

This submission provided data on secondary endpoints for which no formal statistical hypothesis was tested and most of these are presented in this section. While these endpoints are generally considered descriptive and exploratory, in this review, some are used in the risk-benefit assessment of the different dosing regimens as discussed in sections Analysis of Clinical Information Relevant to Dosing Recommendations and 7.5.1 Dose Dependency for Adverse Events.

JIA ACR responses

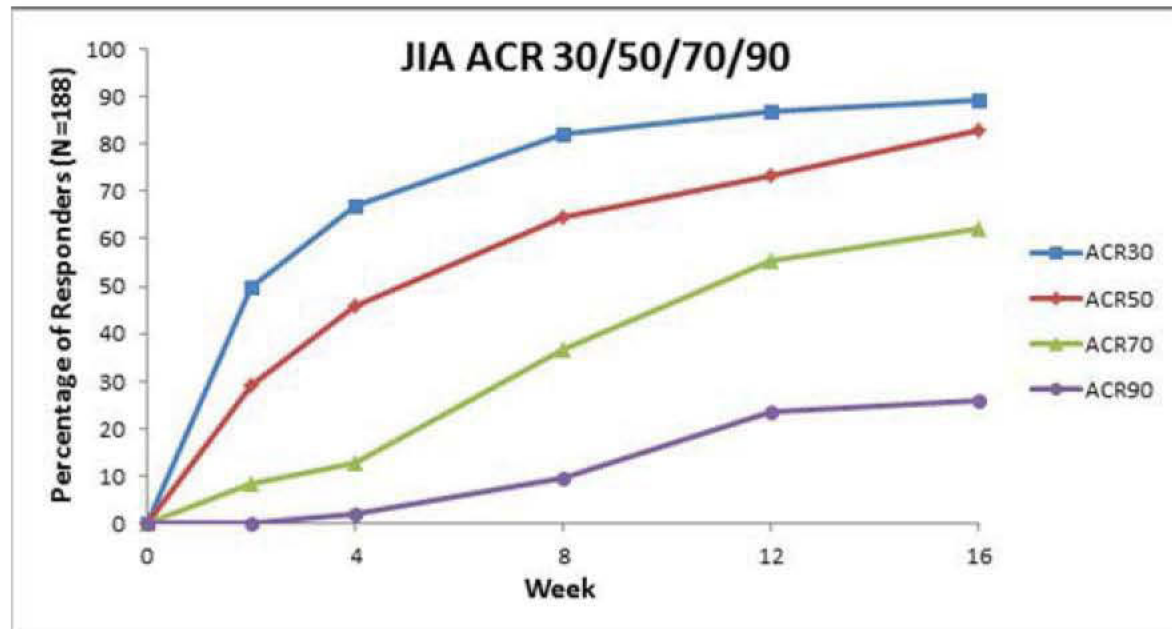
Analyses of the JIA ACR responder rates during Part I (Weeks 0 to 16) are summarized in Table 35 and the kinetics of the clinical responses are presented in Figure 6. These results show overall treatment benefit comparable with the one observed in the Japanese study MRA318JP (see Table 37 and Figure 10), therefore supporting the comparable therapeutic benefit of tocilizumab in pediatric patients with active pJIA both as a monotherapy as well as on the background treatment with methotrexate.

Table 16. JIA ACR Response at Week 16, Study WA19977

JIA ACR Response at Week 16, Study WA19977	
	All TCZ
N	188
ACR30, n (%)	168 (89%)
ACR50, n (%)	156 (83%)
ACR70, n (%)	117 (62%)
ACR90, n (%)	49 (26%)

Source: CSR WA19977, adapted from Tables 10 and etepfrq01 w16 it1 ap1

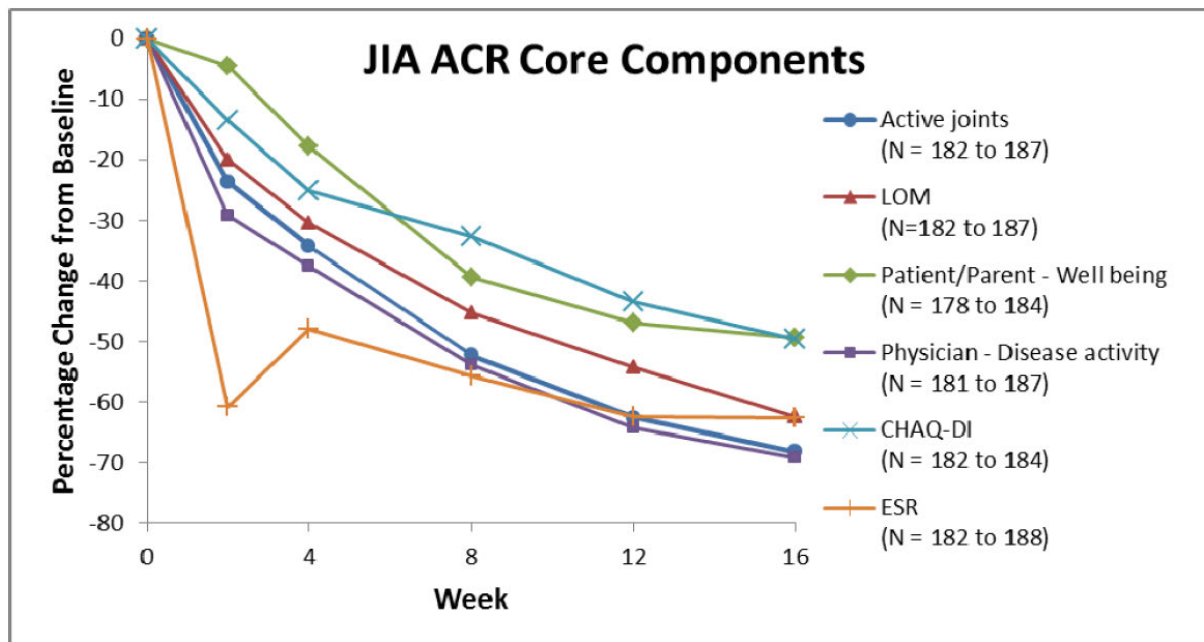
Figure 6. Time Course of JIA ACR Response Week 0 to 16, Study WA19977



Source: CSR WA19977, Figure 3

To investigate the contribution to the observed therapeutic effect on the JIA ACR responder rates as a composite endpoint, the sponsor has analyzed the JIA ACR core components for change from baseline at Week 16 as presented in Figure 7. These analyses indicate that the overall treatment benefit was a result of improvement in all six core JIA ACR components.

Figure 7. JIA ACR Core Component Changes During the Open-Label Lead-in Period, Week 0-16 (Part I), Study WA19977



Source: WA19977 CSR Figure 4

Juvenile Arthritis Disease Activity Score (JADAS)

The JADAS-27 score is a composite score derived from physician global assessment of disease activity, patient/parent global assessment of overall well-being, normalized ESR, and a count of active arthritis at 27 selected joints. The score is measured on a 0-57 scale.

A summary of the JADAS-27 scores at baseline and at Week 16 is presented in Table 17. The baseline disease activity scores were comparable across the treatment groups with a mean of 26. At Week 16 all treatment groups had improved with the highest numerical improvement in the 10 mg/kg dose group, consistent with the JIA ACR response rates shown in Table 35.

As shown in Table 18 below, the change in JADAS-27 at the end of Part II indicates a treatment benefit for patients who were treated with continuous tocilizumab as compared with patients in the placebo-withdrawal group. Also, the treatment benefit was numerically higher in the 10 mg/kg vs. 8 mg/kg dose in patients with body weight <30 kg.

The treatment benefit in improvement of JADAS-27 is consistent with the overall treatment benefit of tocilizumab in pJIA.

Table 17. JADAS-27 at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)

JADAS-27 at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
N	35	34	119	188
Baseline, mean (SD)	28 (13)	28 (9)	25 (9)	26 (10)
Week 16, mean (SD)	9 (9)	12 (10)	8 (7)	8 (8)

Source: Summary of Clinical Efficacy, adapted from Tables 8 etefsum01_j27r_v2b_it1_p1.out, and etefsum01_cj27r_v2_it1_p1.out

Table 18. JADAS-27 Change from Baseline at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)

JADAS-27 Change from Baseline at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)						
	TCZ (N=82)			Placebo (N=81)		
	BW <30 kg		BW ≥30 kg	BW <30 kg		BW ≥30 kg
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg
Randomized and treated, ITT	16	11	55	15	13	53
Change from Baseline, mean (SD)	-21 (19)	-16 (7)	-18 (8)	-19 (16)	-14 (9)	-14 (11)

Source: CSR WA19977, adapted from Table etahsum02_cj27_v3_rx3_it2_p12
 BW-body weight

Pain Visual Analogue Scale (0-100 mm VAS)

Pain was assessed by the patient or parent on a 0-100 mm visual analogue scale (VAS). The baseline pain intensity was comparable across all groups at baseline with a mean of 52 mm. At Week 16, all treatment groups had a decrease in pain intensity with the numerically highest mean change in the 10 mg/kg dose group which is consistent with the overall trend towards a better clinical response in this dose group compared with the 8 mg/kg for patients with body weight < 30 kg.

For patients who enrolled in Part II, placebo-treated patients at the 10 mg/kg dose had a notably higher baseline VAS which contributed to also a numerically notable improvement in pain VAS at Week 40. Despite that however, the overall improvement in pain VAS from baseline to Week 40 as a key secondary endpoint, showed superiority of the pooled tocilizumab versus pooled placebo based on analysis of variance as shown in Table 21.

Table 19. Pain VAS (0-100 mm) at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)

Pain VAS (0-100 mm) at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
N	35	34	119	188
Baseline, mean (SD)	56 (27)	52 (26)	52 (27)	52 (27)
Week 16, mean (SD)	22 (22)	24 (24)	20 (21)	21 (23)

Source: Summary of Clinical Efficacy, adapted from Tables 9 and etefsum01_pnv_nr_v2b_it1_p1.out

Table 20. Pain VAS (0-100 mm) Change from Baseline at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)

Pain VAS (0-100 mm) Change from Baseline at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)						
	TCZ (N=82)			Placebo (N=81)		
	BW <30 kg		BW ≥30 kg	BW <30 kg		BW ≥30 kg
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg
Randomized and treated, ITT	16	11	55	15	13	53
Baseline, mean (SD)	43 (27)	43 (26)	46 (28)	73 (13)	52 (28)	56 (26)
Week 40, mean (SD)	9 (14)	13 (25)	8 (16)	12 (18)	13 (15)	16 (20)
Change from Baseline, mean (SD)	-35 (22)	-30 (34)	-31 (34)	-48 (28)	27 (22)	-26 (27)

Source: CSR WA19977, adapted from Tables etefsum01_pnv_nr_v3b_rx3_it2_p12; etefsum01_pnv_nr_v3b_rx3_it2_p12
 BW-body weight

Table 21. Analysis of Variance of Change from Baseline at Week 40 in Pain VAS (0-100 mm) (ITT Population Part II)

Analysis of Variance of Change from Baseline at Week 40 in Pain VAS (0-100 mm) (ITT Population Part II)		
	All Placebo	All TCZ
N	81	82
Adjusted mean	-22	-32
Difference vs. placebo	-	-0.10
95% CI for the difference		-18, -3
p-value		0.0076

Source: CSR WA19977, adapted from Table 17

Patients with Inactive Disease

Inactive disease was defined as:

- No active joints, and
- No active uveitis, and
- Physician global assessment of ≤ 10 mm, and
- Normal ESR (< 20 mm/h)

In Part I of the study, among the patients with body weight < 30 kg, more patients achieved inactive disease status in the 10 mg/kg dose compared with the 8 mg/kg dose, as shown in Table 22. This observation supports the overall conclusion that the increased exposure with the 10 mg/kg is associated with improved clinically meaningful outcomes compared with the lower exposure of the 8 mg/kg dosing regimen.

Table 22. Proportion of Patients with Inactive Disease at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)

Proportion of Patients with Inactive Disease at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)				
	BW < 30 kg		BW ≥ 30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
N	35	34	119	188
Responder, n (%)	6 (17%)	3 (9%)	17 (14%)	26 (14%)

Source: Summary of Clinical Efficacy, adapted from Tables 9 and etefsum01_pnv_nr_v2b_it1_p1.out

In Part II of the study higher proportions of patients achieved inactive disease status at Week 40 in the continuous tocilizumab treatment groups compared with placebo-withdrawal groups as shown in Table 23 and Table 24 indicating a clinically meaningful benefit of tocilizumab treatment.

Table 23. Proportion of Patients with Inactive Disease at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)

Proportion of Patients with Inactive Disease at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)						
	TCZ (N=82)			Placebo (N=81)		
	BW <30 kg		BW ≥30 kg	BW <30 kg		BW ≥30 kg
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg
Randomized and treated, ITT	16	11	55	15	13	53
Responders, n (%)	6 (38%)	5 (46%)	15 (27%)	2 (13%)	3 (23%)	7 (13%)

Source: CSR WA19977, adapted from Table etrsfrq02_ind_it2_rx3_p2_w40
 BW-body weight

Table 24. Cochran-Mantel-Haenszel Analysis of Proportion of Patients with Inactive Disease at Week 40 in Pain VAS (0-100 mm) (ITT Population Part II)

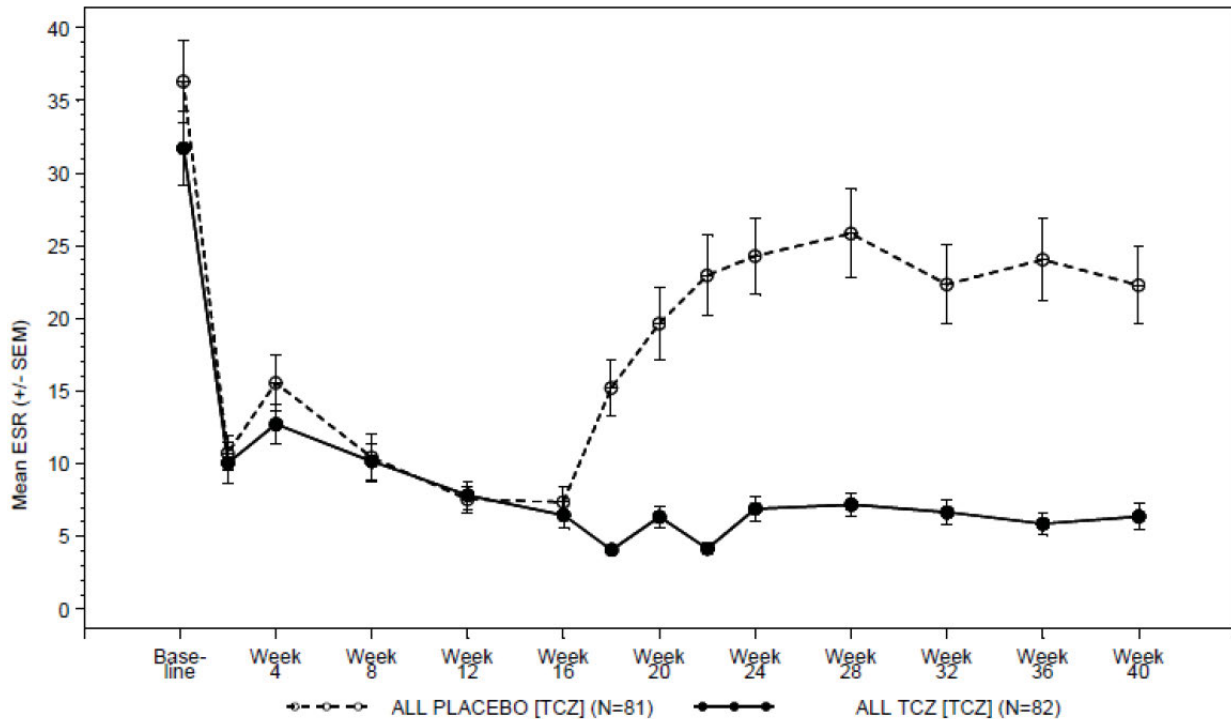
Cochran-Mantel-Haenszel Analysis of Proportion of Patients with Inactive Disease at Week 40 in Pain VAS (0-100 mm) (ITT Population Part II)		
	All Placebo	All TCZ
N	81	82
Responders, n (%)	12 (15%)	26 (32%)
Weighted difference vs. placebo	-	-0.10
95% CI for the weighted difference		0.03, 0.29
p-value		n.s.

Source: CSR WA19977, adapted from Table 18
 n.s.-not statistically significant after adjusting for multiplicity as pre-specified in the protocol

ESR

Treatment with tocilizumab resulted in a notable decline in mean ESR as early as 2 weeks after initiation of therapy followed by sustained low levels through Week 40 for patients who continued tocilizumab therapy in Part II. However, for patients randomized to placebo withdrawal, the ESR has gradually returned close to baseline during Part II, i.e. after withdrawal to placebo as shown in Figure 8, again supporting the treatment effect of tocilizumab.

Figure 8. Line Plot of Mean ESR (mm/h) in Part I and Part II, Study WA19977 (ITT Population Part II)



Source: CSR WA19977, Figure 16

CHAQ-DI Score

In addition to the analyses of CHAQ-DI as a key secondary endpoint discussed above, the sponsor has conducted analyses on the proportion of patients achieving the minimal clinically significant change in CHAQ-DI, defined as a change of at least 0.13 units. These analyses, presented in Table 25 and Table 26 are consistent with the overall treatment benefit of tocilizumab. In addition, the results are consistent with the trend towards numerically better responses in the 10 mg/kg vs. 8 mg/kg dose group in patients with body weight less than 30 kg.

Table 25. Proportion of Patients with Minimally Clinically Important Improvement of at Least 0.13 Units in CHAQ-DI at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)

Proportion of Patients with Minimally Clinically Important Improvement (≥0.13 Units) in CHAQ-DI at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
N	35	34	119	188
Responder, n (%)	28 (80%)	26 (76%)	85 (71%)	139 (74%)

Source: Summary of Clinical Efficacy, adapted from Tables 9 and eteffrq04 haqi nr v2 it1 p1

Table 26. Proportion of Patients with Minimally Clinically Important Improvement of at Least 0.13 Units in CHAQ-DI at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)

Proportion of Patients with Minimally Clinically Important Improvement (≥ 0.13 Units) in CHAQ-DI at Week 40, by Dosing Regimen, Study WA19977 (ITT Population Part II)						
	TCZ (N=82)			Placebo (N=81)		
	BW <30 kg		BW ≥30 kg	BW <30 kg		BW ≥30 kg
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg
Randomized and treated, ITT	16	11	55	15	13	53
Responder, n (%)	13 (87%)	7 (64%)	33 (62%)	8 (56%)	13 (54%)	24 (45%)

Source: CSR WA19977, adapted from Table eteffrq04 haqi nr v3 it2 p12 rx3; BW-body weight

6.1.7 Subpopulations

Analyses of efficacy in subpopulations of patients based on baseline disease and demographic characteristics are presented in this subsection.

The efficacy as measured by JIA ACR30/50/70/90 responses were generally comparable between the males and females and among the different age groups as shown in Table 27, and was consistent with the overall primary and key secondary efficacy. Again noted are the numerically lower responses in the 8 mg/kg dose group in patients with body weight less than 30 kg irrespective of baseline disease characteristics.

Table 27. Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16, by Demographic Characteristic and Dosing Regimen, Study WA19977 (ITT Population)

Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16, by Demographic Characteristics, by Dosing Regimen, Study WA19977 (ITT Population)				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg N=35	TCZ 8 mg/kg N=34	TCZ 8 mg/kg N=119	N=188
Gender				
Males, n	5	10	29	44
JIA ACR30, n (%)	5 (100%)	7 (70%)	25 (86%)	37 (84%)
JIA ACR50, n (%)	5 (100%)	7 (70%)	25 (86%)	37 (84%)
JIA ACR70, n (%)	3 (60%)	4 (40%)	21 (72%)	28 (64%)
JIA ACR90, n (%)	1 (20%)	0 (0%)	9 (31%)	10 (23%)
Females, n	30	24	90	144
JIA ACR30, n (%)	26 (87%)	19 (79%)	86 (96%)	131 (91%)
JIA ACR50, n (%)	23 (77%)	17 (71%)	79 (88%)	119 (82%)
JIA ACR70, n (%)	19 (63%)	10 (42%)	60 (66%)	89 (62%)
JIA ACR90, n (%)	10 (33%)	8 (33%)	21 (23%)	39 (27%)
Age				
≤ 7 years, n	19	17	2	38
JIA ACR30, n (%)	17 (90%)	11 (65%)	2 (100%)	30 (79%)
JIA ACR50, n (%)	16 (84%)	10 (59%)	2 (100%)	28 (74%)
JIA ACR70, n (%)	14 (73%)	7 (41%)	1 (50%)	22 (58%)
JIA ACR90, n (%)	5 (26%)	5 (29%)	0 (0%)	10 (26%)
8-12 years, n	16	16	50	82
JIA ACR30, n (%)	14 (88%)	15 (94%)	49 (98%)	78 (95%)
JIA ACR50, n (%)	12 (75%)	14 (88%)	46 (92%)	72 (88%)
JIA ACR70, n (%)	8 (50%)	7 (44%)	33 (66%)	48 (59%)
JIA ACR90, n (%)	6 (38%)	3 (19%)	12 (24%)	21 (26%)
≥ 13 years, n	0	1	67	68
JIA ACR30, n (%)	-	0 (0%)	60 (90%)	60 (88%)
JIA ACR50, n (%)	-	0 (0%)	56 (84%)	56 (82%)
JIA ACR70, n (%)	-	0 (0%)	47 (70%)	47 (69%)
JIA ACR90, n (%)	-	0 (0%)	18 (27%)	18 (27%)

Source: Summary of Clinical Efficacy, adapted from Tables 33, 34, 35, 36

Patients with disease duration longer than 2 years had numerically lower but generally comparable responses to patients with shorter disease duration as shown in Table 28. This is not unexpected and is consistent with a more refractory disease.

Table 28. Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16, by Disease Characteristics, by Dosing Regimen, Study WA19977 (ITT Population)

Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16, by Disease Characteristics, by Dosing Regimen, Study WA19977 (ITT Population)				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg N=35	TCZ 8 mg/kg N=34	TCZ 8 mg/kg N=119	N=188
Disease duration				
< 2 years, n	11	11	40	62
JIA ACR30, n (%)	10 (91%)	9 (82%)	38 (95%)	57 (92%)
JIA ACR50, n (%)	9 (82%)	9 (82%)	35 (88%)	53 (86%)
JIA ACR70, n (%)	8 (73%)	8 (73%)	30 (75%)	46 (74%)
JIA ACR90, n (%)	5 (46%)	5 (46%)	14 (35%)	24 (39%)
≥ 2 years, n	24	23	79	126
JIA ACR30, n (%)	21 (88%)	17 (74%)	73 (92%)	111 (88%)
JIA ACR50, n (%)	19 (79%)	15 (65%)	69 (87%)	103 (82%)
JIA ACR70, n (%)	14 (58%)	6 (26%)	51 (65%)	71 (56%)
JIA ACR90, n (%)	6 (25%)	3 (13%)	16 (20%)	25 (20%)
Rheumatoid factor (RF) Status				
RF positive	4	2	48	54
JIA ACR30, n (%)	3 (75%)	2 (100%)	43 (90%)	48 (89%)
JIA ACR50, n (%)	3 (75%)	2 (100%)	43 (90%)	48 (89%)
JIA ACR70, n (%)	3 (75%)	2 (100%)	38 (79%)	43 (80%)
JIA ACR90, n (%)	2 (50%)	0 (0%)	15 (31%)	17 (32%)
RF negative	31	30	65	126
JIA ACR30, n (%)	28 (90%)	22 (73%)	62 (95%)	112 (89%)
JIA ACR50, n (%)	25 (81%)	21 (70%)	55 (85%)	101 (80%)
JIA ACR70, n (%)	19 (61%)	12 (40%)	38 (59%)	69 (55%)
JIA ACR90, n (%)	9 (29%)	8 (27%)	13 (20%)	30 (24%)
RF missing	0	2	6	8
JIA ACR30, n (%)	-	2 (100%)	6 (100%)	8 (100%)
JIA ACR50, n (%)	-	1 (50%)	6 (100%)	7 (88%)
JIA ACR70, n (%)	-	0 (0%)	5 (83%)	5 (63%)
JIA ACR90, n (%)	-	0 (0%)	2 (33%)	2 (25%)

Source: Summary of Clinical Efficacy, adapted from Tables 33, 34, 35, 36

Additional subpopulation analyses

Analyses of efficacy in subpopulations of patients based on the baseline stratification variables of background MTX and oral CS use and prior biologic use are presented in this subsection.

Background Methotrexate (MTX)

The eligibility criteria of study WA19977 selected for patients with an inadequate response to MTX due to lack of efficacy or toxicity and patients were allowed to on stable doses of MTX but were not required. Therefore at baseline 79% of patients were taking concurrent MTX. Because MTX use was a pre-specified stratification factor, MTX users were approximately equally distributed between the patients who had continuous tocilizumab or placebo exposure in Part II of the study as shown in Table 30.

Patients who had continuous tocilizumab had numerically better outcomes compared with placebo-withdrawal patients in Part II in clinical response measures regardless of MTX background therapy as seen in Table 30, which is consistent with the overall differences seen in the primary analyses.

Importantly however, patients taking background methotrexate demonstrated numerically higher JIA ACR30/50/70/90 responses and lower JIA ACR30 flare rates as compared with patients who were not on background MTX both at Week 16 (Table 29) and at Week 40 (Table 30). At Week 40 higher proportion of patients not on MTX flared compared with patients on background MTX which is particularly notable in the placebo-withdrawal group as these patients were on no background therapy as seen in Table 30.

To further investigate these findings and the potential interaction between of MTX use and tocilizumab treatment, the sponsor has conducted logistic regression analysis of the proportion of patients with JIA ACR30 flare by background MTX and found that the effect of background MTX was independent of the effect of tocilizumab as shown in Table 31.

While these observations were not a part of the pre-specified efficacy analyses, they indicate that MTX has an independent additive therapeutic benefit to tocilizumab in this patient population which may warrant inclusion in labeling. For recommendations on the labeling revisions, see section Labeling Recommendations.

Table 29. Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Background MTX Use at Baseline, by Dosing Regimen, Study WA19977 (ITT Population)

Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Background MTX Use at Baseline, by Dosing Regimen, Study WA19977 (ITT Population Part I)				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg N=35	TCZ 8 mg/kg N=34	TCZ 8 mg/kg N=119	N=188
Baseline MTX Use				
Yes, n	29	30	89	148
JIA ACR30, n (%)	26 (90%)	24 (80%)	85 (96%)	135 (91%)
JIA ACR50, n (%)	23 (79%)	22 (73%)	79 (89%)	124 (84%)
JIA ACR70, n (%)	18 (62%)	13 (43%)	64 (72%)	95 (64%)
JIA ACR90, n (%)	9 (31%)	7 (23%)	29 (33%)	45 (30%)
No, n	6	4	30	40
JIA ACR30, n (%)	5 (83%)	2 (50%)	26 (87%)	33 (83%)
JIA ACR50, n (%)	5 (83%)	2 (50%)	25 (83%)	32 (80%)
JIA ACR70, n (%)	4 (67%)	1 (25%)	17 (57%)	22 (55%)
JIA ACR90, n (%)	2 (33%)	1 (25%)	1 (3%)	4 (10%)

Source: CSR WA19977, adapted from Table etepfrq01_w16_bmtx_it1_ap1

Table 30. Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Background MTX Use at Baseline (ITT Population Part II)

Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Background MTX Use at Baseline (ITT Population Part II)				
MTX use	All placebo		All TCZ	
	Yes	No	Yes	No
n (%)	64 (79%)	17 (21%)	67 (82%)	15 (18%)
JIA ACR30 Flare, n (%)	25 (39%)	14 (82%)	13 (19%)	8 (53%)
JIA ACR30 Response, n (%)	39 (61%)	5 (29%)	53 (79%)	8 (53%)
JIA ACR50 Response, n (%)	38 (59%)	4 (24%)	52 (78%)	8 (53%)
JIA ACR70 Response, n (%)	30 (47%)	4 (24%)	45 (67%)	8 (53%)
JIA ACR90 Response, n (%)	18 (28%)	1 (6%)	32 (48%)	5 (33%)

Source: Summary of Clinical Efficacy, adapted from Tables 19, 20 and etepfrq05_w40_bmtx_rx3_it2_ap12

Table 31. Logistic Regression Analysis of the Proportion of Patients with JIA ACR30 Flare by Background MTX at Week 16 Interaction (ITT Population Part II)

Logistic Regression Analysis of the Proportion of Patients with JIA ACR30 Flare by Background MTX at Week 16 Interaction (ITT Population Part II)		
Effect/Covariate included in the model	Odds Ratio, (95% CI)	p-value
Treatment effect (reference All Placebo, n=81) All tocilizumab, n=82	0.39 (0.2, 0.9)	0.021
Background MTX use (reference Yes, n=130) No use, n=33	8.5 (2.2, 33.5)	0.002
Background CS use (reference No, n=92) Yes, n=71	1.76 (0.9, 3.6)	0.124
Treatment by MTX use at Week 16 interaction All tocilizumab	0.55 (0.1, 3.3)	0.507

Source: Summary of Clinical Efficacy, adapted from Table 21

Background Oral Corticosteroids (CS)

The protocol allowed but did not require patients to take background oral CS one half of the patients were taking oral CS at baseline. As oral CS were the second pre-specified stratification variable at randomization they were approximately equally distributed between the patients who had continuous tocilizumab or placebo exposure in Part II of the study as shown in Table 32. Regardless of the background CS use, the clinical responses were consistent with the overall primary efficacy comparing continuous TCZ and placebo-withdrawal groups.

In addition, in contrast to the observation of the additive effect of background MTX, oral CS did not appear to have additional clinical benefit to tocilizumab as the proportions of patients with improvements in the key clinical response criteria were comparable between those who were and those who were not taking background oral CS as shown in Table 32 and Table 33.

Table 32. Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Background Oral Corticosteroid (CS) Use at Baseline (ITT Population Part II)

Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Background Oral Corticosteroid (CS) Use at Baseline (ITT Population Part II)				
Oral CS use	All placebo		All TCZ	
	Yes	No	Yes	No
n (%)	38 (47%)	43 (53%)	33 (40%)	49 (60%)
JIA ACR30 Flare, n (%)	21 (55%)	18 (42%)	8 (24%)	13 (27%)
JIA ACR30 Response, n (%)	18 (47%)	26 (61%)	24 (73%)	37 (76%)
JIA ACR50 Response, n (%)	17 (45%)	25 (58%)	24 (73%)	36 (74%)
JIA ACR70 Response, n (%)	14 (47%)	20 (47%)	23 (70%)	30 (61%)
JIA ACR90 Response, n (%)	5 (13%)	14 (33%)	16 (49%)	21 (43%)

Source: Summary of Clinical Efficacy, adapted from Tables 22 and etepfrq05_w40_bocs_rx3_it2_ap12

Table 33. Logistic Regression Analysis of the Proportion of Patients with JIA ACR30 Flare with Treatment by Background Oral CS and at Week 16 Interaction (ITT Population Part II)

Logistic Regression Analysis of the Proportion of Patients with JIA ACR30 Flare with Treatment by Background Oral CS and at Week 16 Interaction (ITT Population Part II)		
Effect/Covariate included in the model	Odds Ratio, (95% CI)	p-value
Treatment effect (reference All Placebo, n=81) All tocilizumab, n=82	0.48 (0.2, 1.2)	0.130
Background MTX use (reference Yes, n=130) No use, n=33	6.03 (2.5, 14.5)	<0.0001
Background CS use (reference No, n=92) Yes, n=71	2.38 (0.9, 6.1)	0.073
Treatment by Oral CS use at Week 16 interaction All tocilizumab	0.49 (0.1, 2.0)	0.327

Source: Summary of Clinical Efficacy, adapted from Table 23

Prior Biologics Use

About 32% (61/188) of patients enrolled in study WA19977 have had prior exposure to biologic agents which was allowed in the protocol. The clinical responses were consistent with the overall primary efficacy comparing continuous TCZ and placebo-withdrawal groups as shown in Table 34.

However, patients who have been exposed to prior biologics had generally lower clinical responses and higher flare rates than biologic-naïve patients which is consistent with the scenario where patients who have been treated with prior biologic therapies constitute a more refractory patient population.

Table 34. Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Previous Biologic Use at Baseline (ITT Population Part II)

Proportion of Patients with a JIA ACR30/50/70/90 Responses at Week 40, by Previous Biologic Use at Baseline (ITT Population Part II)				
	All placebo		All TCZ	
Prior biologic use	Yes	No	Yes	No
n (%)	23 (28%)	58 (72%)	27 (33%)	55 (67%)
JIA ACR30 Flare, n (%)	18 (78%)	21 (36%)	12 (44%)	9 (16%)
JIA ACR30 Response, n (%)	6 (26%)	38 (66%)	15 (56%)	46 (84%)
JIA ACR50 Response, n (%)	5 (22%)	37 (64%)	14 (52%)	46 (84%)
JIA ACR70 Response, n (%)	2 (9%)	32 (55%)	13 (48%)	40 (73%)
JIA ACR90 Response, n (%)	2 (9%)	17 (29%)	5 (19%)	32 (58%)

Source: Summary of Clinical Efficacy, adapted from Tables 24 and etepfrq05_w40_bbio_rx3_it2_ap12

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Over the first 16 weeks of the study, JIA ACR responses were lower in the <30 kg group receiving 8 mg/kg TCZ compared to 10 mg/kg TCZ as shown in Table 35 and Figure 9 and a higher proportion of patients in the 8 mg/kg group (9/34) failed to progress to Part 2 for reasons other than safety compared to the 10 mg/kg group (4/35). These differences were not dependent on gender, age, or disease duration as discussed in section 6.1.7 Subpopulations above.

Table 35. JIA ACR Response Rates During the Open-Label Lead-in Period, Week 0-16 (Part I), Study WA19977

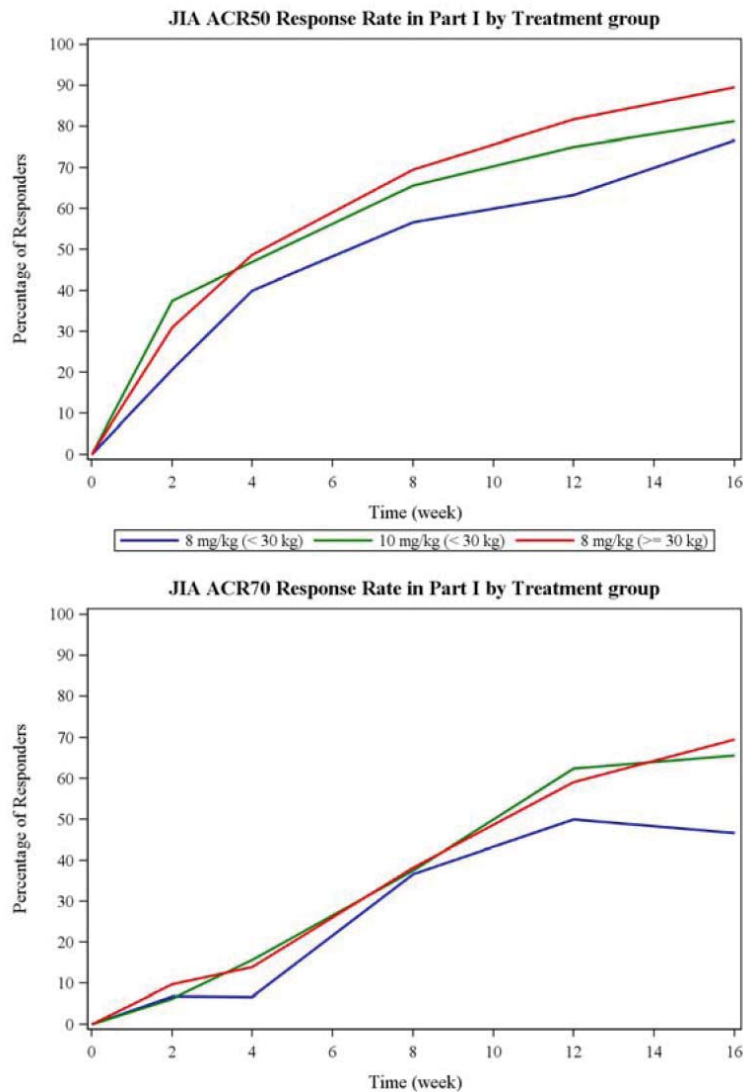
JIA ACR Response at Week 16, by Dosing Regimen, Study WA19977 (ITT Population)				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
N	35	34	119	188
ACR30, n (%)	31 (89%)	26 (77%)	111 (93%)	168 (89%)
ACR50, n (%)	28 (80%)	24 (71%)	104 (87%)	156 (83%)
ACR70, n (%)	22 (63%)	14 (41%)	81 (68%)	117 (62%)
ACR90, n (%)	11 (31%)	8 (24)	30 (25%)	49 (26%)

Source: CSR WA19977, adapted from Tables 10 and etepfrq01 w16 it1 ap1

The lower response rate in the 8 mg/kg (BW <30 kg group) is likely secondary to lower drug exposure. These observations are consistent with the exposure-response analyses and simulations from study MRA318JP as discussed in section 4.4.4. Dose-Selection Rationale above. In contrast, the overall efficacy of the 10 mg/kg <30 kg BW group was similar to the 8 mg/kg ≥30 kg BW group.

Further PK analyses from study WA19977 determined that the 10 mg/kg dose in children weighing <30 kg provides more comparable exposure to that of the 8 mg/kg dose in children with a body weight ≥30 kg.

Figure 9. JIA ACR Response by Treatment Group at Week 16, Study WA19977



Source: Summary of Clinical Pharmacology, Figure 6

The comparison of efficacy outcome (JIA ACR30/50/70/90) by treatment group confirmed that efficacy achieved for the 10 mg/kg dose in children with a body weight < 30 kg was comparable to that for the 8 mg/kg dose in children weighing ≥30 kg. The sponsor-conducted analyses of JIA ACR responses by PK exposure quartiles further supported the notion that lower PK exposure resulted in lower clinical efficacy as shown in Table 36.

Table 36. Summary of TCZ PK Exposure Parameters by ACR Response Status to Week 16 for All Patients (Part I)

Summary of TCZ PK Exposure Parameters by ACR Response Status to Week 16 for All Patients (Part I)				
	JIA ACR30	JIA ACR50	JIA ACR70	JIA ACR90
Non-Responders, n	13	25	62	128
AUC _{wk12-16} , µg·day/mL, mean (SD)	850 (394)	922 (401)	1032 (387)	1075 (377)
C _{max_wk12} , µg/mL, mean (SD)	156 (46)	161 (40)	169 (37)	171 (36)
C _{wk16} , µg/mL, mean (SD)	2.6 (4)	3.6 (6)	4.4 (7)	5.4 (7)
Responders, n	164	152	115	49
AUC _{wk12-16} , µg·day/mL, mean (SD)	1113 (374)	1122 (371)	1127 (375)	1143 (392)
C _{max_wk12} , µg/mL, mean (SD)	175 (37)	175 (37)	176 (38)	180 (43)
C _{wk16} , µg/mL, mean (SD)	5.8 (8)	5.9 (8)	6.2 (8)	6.1 (8)

Source: Summary of Clinical Pharmacology, adapted from Table 7

In summary, the sponsor-proposed dosing recommendation of:

- 8 mg/kg q 4 weeks for patients with body weight of 30 kg and over and
- 10 mg/kg q 4 weeks for patients with body weight of less than 30 kg

appears supported by the available clinical efficacy and PK data.

The dose-dependency of safety in the as it relates to dosing recommendations is discussed in section 7.5.1 Dose Dependency for Adverse Events below.

6.1.9 Discussion of Persistence of Efficacy

Persistence of efficacy was evaluated in the responders from the open label lead-in period Part I who continued on tocilizumab blinded treatment during Part II of the study. A summary plot of ACR30 responder rates over time is provided in Figure 4 above, indicating that the majority of patients who responded at Week 16 and continued to receive tocilizumab for the next 24 weeks retained ACR30 responder status. Similar trends were observed for the ACR50/70/90 responder rates. Definitive conclusions however, cannot be drawn from the efficacy data in study WA19977 due to study design limitations, such as open-label lead-in period and drop out of non-responders by Week 16 and the lack of control group for comparative analysis of persistence of efficacy. However, the overall results support the conclusion that tocilizumab treatment remains effective over time.

6.1.10 Additional Efficacy Issues/Analyses

Additional efficacy data are derived from the supportive studies MRA319/319JP and presented in this section.

Endpoints:

The efficacy measurements in studies MRA319/319JP included:

- the JIA core set
- CRP
- Pain (VAS)

The primary efficacy outcome measure of both study MRA318JP and the long term extension study MRA319JP was the percentage of patients showing a JIA ACR30 response. In study MRA318JP the primary endpoint was at the last observation day, i.e. at the Week 12 visit. In the long term extension study, efficacy was evaluated using data for the period from before the first TCZ infusion in MRA318JP until the last observation day. The baseline for analysis of both studies was the same.

Secondary efficacy measures were the time courses of JIA ACR30, 50 and 70 responses, of the JIA core set components, of CRP and of pain.

Summary of Results:

The primary and secondary results in studies MRA319/319JP are summarized in Table 37. Since these studies are open label uncontrolled studies, interpretation of the results is limited due to lack of controlled data; however the overall results indicate efficacy consistent with the one seen during the open-label lead-in period (Part I) in study WA19977, where the JIA ACR30 responses rates were on average 89% as shown in Table 35 above.

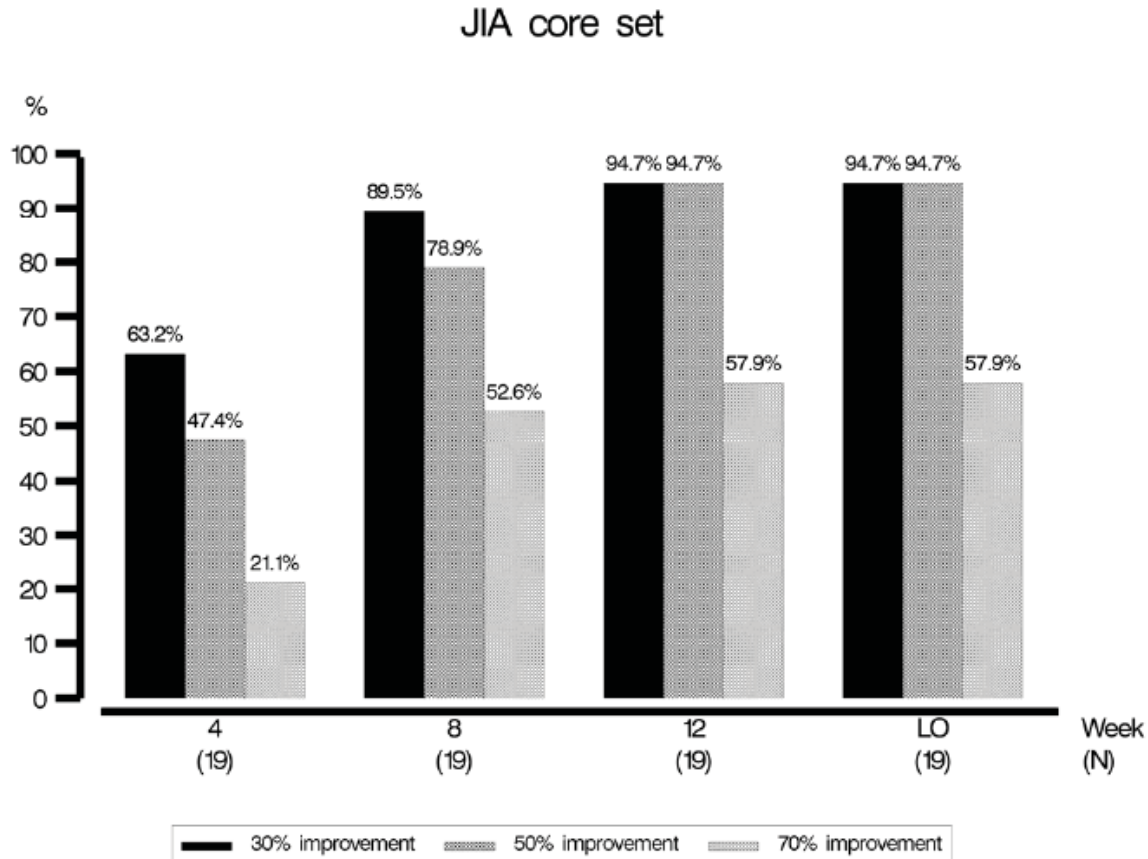
Table 37. Summary of Efficacy Assessments in Studies MRA318JP and MRA319JP.

Summary of Efficacy Assessments in Supportive Monotherapy Studies MRA318JP and MRA319JP			
Study	N	Primary endpoint: JIA ACR30	Secondary endpoints
MRA318JP	19	94.7% (Week 12)	JIA ACR50: 94.7% JIA ACR70: 57.9%
MRA319JP	19	94.1% (Week 24)	JIA ACR50: 94.1% JIA ACR70: 94.1%

Source: CSR MRA318JP and MRA319JP

Figure 10 is a graphic representation of the time course of proportions of patients with 30%, 50%, and 70% improvement in the ACR JIA core set in response to treatment with TCZ 8 mg/kg q4 weeks as a monotherapy and as early as 4 weeks. The results were consistent across the five study sites.

Figure 10. Time Course of JIA ACR 30, 50 and 70 Responders in Study MRA318JP



Source: CSR MRA318JP

The consistent improvement was also observed in each of the JIA core set components in secondary analyses.

MRA319JP:

Range of follow-up in study MRA319JP is 0.35-3.5 years. By week 168, all 15 remaining patients had achieved a JIA ACR30 response, and 93.3% (14/15 patients) had achieved a ACR70% response. In addition, the average corticosteroid dose per 12 weeks decreased over the course of treatment with tocilizumab

While the efficacy data from the Japanese study MRA318/319JP is open-label and uncontrolled, it is consistent with the findings of the primary analysis of efficacy from study WA19977 and supportive of the overall efficacy of TCZ in the population of patients with pJIA.

Analyses of the efficacy data with respect to body weight and dose in study MRA318JP are presented in Section 4.4.4. Dose-Selection Rationale.

7 Review of Safety

7.1 Methods

The submission contains clinical safety data on Adverse Events (AEs), Serious Adverse Events (SAEs), and adverse events of interest. The applicant has used the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1 for assigning preferred terms to AEs, diseases, and surgical and medical procedures for this Summary of Clinical Safety and the 120 Day Safety Update. Abnormal laboratory data were classified according to the common toxicity criteria (CTC) grading system (version 3).

Due to the randomized withdrawal design of the study, some patients had an interruption of tocilizumab regimen while randomized to placebo withdrawal in Part II followed by re-initiation of tocilizumab. To account for the different duration of exposure, the applicant has presented AE rates as a function of total patient-years of observation (i.e., duration on trial treatment) and expressed as rates of events per 100 patient-years. This presentation may provide useful information that allows for comparison of AEs over time and also across the tocilizumab development programs for adult RA and sJIA since they employed the same adjustment. This approach however, has one limitation; it assumes steady rate of AEs over time which may not be true for events with long latency such as malignancy and opportunistic infections. However such events were not reported in this program.

Due to these considerations the safety presentation in this review follows the following format:

- Safety in Part I for head-to-head comparisons of safety data across the treatment regimens (8 mg/kg for all patients ≥ 30 kg and 8 mg/kg or 10 mg/kg for patients < 30 kg) during the open label lead-in period (Part I) where all patients had comparable exposure with a mean of 16 weeks.
- Safety in the All Exposure Population (Part I, Part II, and Part III as of the last clinical data cut-off).

Additional analyses were conducted for comparing the safety profile of tocilizumab in pJIA development program with the safety profile of tocilizumab in the already approved indications, adult RA and systemic JIA (sJIA).

The 120 Day Safety Update contained clinical safety data on cumulative safety from the open-label extension in study WA19977 up to May 03, 2012.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary source of safety data is from confirmatory study WA19977, with supportive data provided from the two Japanese studies MRA318JP and MRA319JP described in section 9.4 Individual Study Reports.

7.1.2 Categorization of Adverse Events

Adverse events were coded by using the MedDRA version 14.1. All clinical AEs encountered during the clinical study will be reported on the AE page of the CRF. Intensity of AEs will be graded on a three -point scale [mild, moderate, severe] and reported in detail on the CRF.

- Mild discomfort noticed but no disruption of normal daily activity.
- Moderate discomfort sufficient to reduce or affect daily activity.
- Severe inability to work or perform normal daily activity

SAEs were defined as any event that resulted in death, was life-threatening, resulted in a persistent or significant disability or incapacity, required in-patient hospitalization or prolongation of existing hospitalization, or resulted in a congenital anomaly or birth defect. In addition, other important medical events were considered SAEs if they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition.

For the purposes of this study, the following were not considered an SAE:

- Elective hospitalizations or surgical procedures that are the result of a patient's pre-existing condition(s) which have not worsened since receiving study medication. Examples may include, but are not limited to: joint replacement surgery, physical therapy rehabilitation, diagnostic testing. Such events must still be recorded as adverse events in the eCRF.
- Hospitalization for articular/peri-articular manifestations of pJIA. Such events must be recorded as adverse events in the eCRF.
- Hospitalization to receive study medication such as infusions of tocilizumab unless it is prolonged (more than 24 hours) due to a safety issue (including infusion associated adverse events).

Related Serious Adverse Events (SAEs) were collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated Serious Adverse Events must be collected and reported from the time of consent throughout the study and for up to 12 weeks after the last dose of study medication.

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

Since design of the confirmatory study WA19977 (three part randomized withdrawal) was different from the design of the Japanese supportive studies (open label) the safety data were reviewed separately rather than pooled.

7.2 Adequacy of Safety Assessments

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

The tocilizumab exposure for Part I and the overall exposure in study WA19977 are summarized in Table 38 for both the original submission and updated with the exposure data in the 120-day safety update.

In Part I of the study all patients were treated with tocilizumab and tocilizumab exposure was comparable across all treatment groups and dose regimens with a mean of approximately 0.3 years as shown in Table 38. Safety analyses during this period were used to compare safety profile of the different dosing regimens head-to-head.

While the duration of exposure in this pediatric program is relatively small, the overall exposure and duration are generally comparable with the exposure in pJIA development programs of already approved products and meets the Division's expectations of a safety database and exposure to allow for a qualitative assessment of safety in the context of previously defined safety profile of tocilizumab in adult RA. Of note, the sponsor has used the duration in study instead of exposure in years for calculating the event rates in patient-years for the safety analyses. This approach is acceptable as it was applied uniformly throughout the safety analyses and allows for comparison within the program and across the adult RA and sJIA programs. However, it may not be entirely reliable for comparison to other products where the event rates may have been determined based on actual exposure, i.e. exposure-adjusted event rates.

Table 38. Summary of Exposure to Tocilizumab, Study WA19977

Summary of Exposure to Tocilizumab, in Study WA19977					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Part I, TCZ exposure up to Week 16					
Enrolled, n	35	-	34	119	188
TCZ Exposure, PY	11	-	10	36	58
Duration in study, PY	12	-	11	37	60
Mean duration of exposure, years	0.3	-	0.3	0.3	0.3
All Exposure Population As of 11/04/2011 (Original submission)					
Enrolled, n	28	7	34	119	188
TCZ Exposure, PY	23	9	25	120	177
Duration in study, PY	25	9	27	124	184
Mean duration of exposure, years	0.9	1.2	0.8	1.0	1.0
All Exposure Population As of 05/03/2012 (120 day safety update)					
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
Mean duration of exposure, years	1.2	1.6	1.1	1.4	1.4
Source: CSR WA19977 and 120-Day Safety Update, adapted from Tables std1_durexp_1; std1_durexp_ae; stdm11_durexp; BW-body weight; PY- patient-years; *In Part III only, 12 patients had their TCZ dose decreased to 8 mg/kg as their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits					

7.2.2 Explorations for Dose Response

The pJIA development program tested the following dosing regimens:

- 8 mg/kg for all patients ≥30 kg and for some (randomized) patients <30 kg
- 10 mg/kg for the remaining patients <30 kg

Dose response based on these dosing regimens was reviewed in section 7.5.1 Dose Dependency for Adverse Events with regard to safety and in section Analysis of Clinical Information Relevant to Dosing Recommendations with regard to efficacy.

7.2.3 Special Animal and/or In Vitro Testing

No specific animal and/or in vitro testing was considered necessary to further explore the safety profile of tocilizumab in this development program. Therefore, no special animal and/or in vitro testing was submitted or expected for this sBLA.

7.2.4 Routine Clinical Testing

The type and frequency of the routine clinical testing in the confirmatory study WA19977 and the supporting Japanese studies MRA318JP and MRA319JP were generally acceptable and are described in section Individual Study Reports.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

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

Tocilizumab is the first in class of biologics targeting IL-6 signaling and no safety information from other IL-6 targeting therapies is available. The relative safety in patients with pJIA however is compared with the safety profile of tocilizumab in the already approved indications, rheumatoid arthritis (RA) and systemic JIA (sJIA) in section 7.7 Additional Submissions / Safety Issues.

7.3 Major Safety Results

Safety Overview

Study WA19977

In the all exposure population, which includes all the safety data from the entire study up until the clinical data cut-off date of May 03, 2012 there were no deaths and the summary of the SAEs, AEs leading to withdrawal and dose modification are presented in Table 39. As shown in the table, during the open-label lead-in period (Part I), among the patients with body weight less than 30 kg, a higher proportion of patients in the 10 mg/kg group experienced AEs, infections, SAEs, and serious infections compared with the 8 mg/kg dose group, whereas no SAEs or serious infections occurred in the 8 mg/kg group. Of note, the small number of SAEs in the 10 mg/kg dose group, both of which infections characteristic for the underlying patient population, make definitive conclusions on the dose-dependency difficult. Further, the rates in the 10 mg/kg group were comparable to the rates observed in the heavier patients treated with 8 mg/kg dose. With longer-term exposure, as of the 120-day safety update, the exposure-adjusted incidence rates for overall AEs and infections reversed and serious infections also accrued in the in the 8 mg/kg dose group. The exposure-relationship for safety was further explored and discussed in section 7.5.1 Dose Dependency for Adverse Events.

In summary, the inconsistent trends in the overall AEs between short-term and longer-term tocilizumab exposures, and the relatively small number of SAEs and serious infections, do not indicate a clear dose-dependent increases between the 10 mg/kg and 8 mg/kg dose regimens in patients with body weight less than 30 kg. Conclusions on the

dose-dependency in the heavier patients with a body weight of 30 kg and over cannot be made reliably as only one dosing regimen, 8 mg/kg, was tested in this group.

The overall safety results from the supporting Japanese studies MRA318/319JP were consistent with the results from Study WA19977.

Table 39. Summary of Safety in Study WA19977, All Exposure Population

Summary of Safety in Study WA19977, All Exposure Population					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Part I, TCZ exposure up to Week 16					
Enrolled, n	35	n.a.	34	119	188
TCZ Exposure, PY	11	n.a.	10	36	58
All AEs, n of events, (% patients)	53 (77%)	n.a.	56 (65%)	223 (63%)	332 (66%)
<i>Infections and Infestation, n (% patients)</i>	22 (49%)	n.a.	18 (32%)	68 (42%)	108 (42%)
SAEs, n of events, (% patients)	2 (6%)	n.a.	-	5 (4%)	7 (4%)
<i>Serious infections, n of events, (% patients)</i>	2 (6%)	n.a.	-	2 (2%)	4 (2%)
AEs leading to withdrawal, n (%)	-	n.a.	1 (3%)	2 (2%)	3 (2%)
All Exposure Population As of 11/04/2011 (Original submission)					
Enrolled, n	28	7	34	119	188
TCZ Exposure, PY	23	9	25	120	177
Duration in study, PY	25	9	27	124	184
All AEs, n of events (rate per 100 PY)	110 (446)	25 (288)	128 (472)	622 (502)	885 (480)
<i>Infections and Infestation, n (rate/100 PY)</i>	49 (199)	6 (69)	48 (177)	199 (161)	302 (164)
SAEs, n of events (rate per 100 PY)	3 (12)	-	2 (7)	18 (15)	23 (13)
<i>Serious infections, n (rate/100 PY)</i>	3 (12)	-	1 (4)	5 (4)	9 (5)
AEs leading to withdrawal	1	-	2	3	6
AEs leading to dose modification, n (% patients)	11 (29%)	1 (14%)	3 (6%)	16 (11%)	31 (13%)
<i>Infections and Infestation, n (% patients)</i>	6 (21%)	-	2 (6%)	11 (8%)	20 (9%)
All Exposure Population As of 05/03/2012 (120-day safety update)					
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
All AEs, n of events (rate per 100 PY)	113 (399)	60 (321)	180 (471)	778 (458)	1131 (443)
<i>Infections and Infestation, n (rate/100 PY)</i>	51 (180)	21 (112)	78 (204)	263 (155)	413 (162)
SAEs, n of events (rate per 100 PY)	4 (14)	1 (5)	3 (8)	20 (12)	28 (11)
<i>Serious infections, n (rate/100 PY)</i>	3 (11)	1 (5)	2 (5)	6 (4)	12 (5)
AEs leading to withdrawal	2	-	2	3	7
AEs leading to dose modification, n (% patients)	11 (30%)	2 (17%)	4 (9%)	25 (14%)	42 (15%)
<i>Infections and Infestation, n (% patients)</i>	8 (26%)	-	3 (9%)	18 (11%)	29 (12%)
Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1 BW-body weight; PY- patient-years; *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits					

7.3.1 Deaths

There were no deaths reported in the definitive study WA19977 or the supportive Japanese studies MRA318JP and MRA319JP.

7.3.2 Non-Fatal Serious Adverse Events

Part I

Non-fatal SAEs from study WA19977 are presented first for the open label lead-in period, Part I, up to Week 16 (Table 40) to allow for head-to-head comparisons among the treatment regimens. The most common SAEs were in the system organ class (SOC) of Infections and Infestations, with two cases of bronchitis in the 10 mg/kg dose group, one case of pneumonia and one case of cellulitis in the 8 mg/kg dose group, both in patients over 30 kg. This observation is consistent with the overall AEs (see section 7.4.1 Common Adverse Events) and the known safety profile of tocilizumab in adult RA patients and patients with sJIA. Definitive conclusions on potential dose-dependency (10 mg/kg vs. 8 mg/kg in the patients with body weight less than 30 kg) is difficult to make based on the small number of events and the nature of events (bronchitis) which are expected in this patient population. Further discussion on the exposure-response analyses for safety is provided in section 7.5.1 Dose Dependency for Adverse Events.

Table 40. Summary of Non-Fatal Serious AEs up to Week 16, Part I, Study WA19977

Summary of Non-Fatal Serious AEs up to Week 16, Part I, Study WA19977					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	35	n.a.	34	119	188
TCZ Exposure, PY	11	n.a.	10	36	58
No. of patients with ≥ 1 SAE, n (%)	2 (6%)	n.a.	-	5 (4%)	7 (4%)
Total No. of events SAEs, n	2	n.a.	-	6	8
Event by SOC and PT, n (% of patients)					
Infection and Infestation	2 (6%)	n.a.	-	2 (2%)	4 (2%)
<i>Bronchitis</i>	2 (6%)	n.a.	-	-	2 (1%)
<i>Cellulitis</i>	-	n.a.	-	1 (1%)	1 (<1%)
<i>Pneumonia</i>	-	n.a.	-	1 (1%)	1 (<1%)
Gastrointestinal Disorders	-	n.a.	-	1 (1%)	1 (<1%)
<i>Constipation</i>	-	n.a.	-	1 (1%)	1 (<1%)
Nervous System Disorders	-	n.a.	-	1 (1%)	1 (<1%)
<i>Benign intracranial hypertension</i>	-	n.a.	-	1 (1%)	1 (<1%)
Hepatobiliary	-	n.a.	-	2 [†] (1%)	2 [†] (<1%)
<i>Cholangitis sclerosing</i>	-	n.a.	-	1 (1%)	1 (<1%)
<i>Hypertransaminasemia</i>	-	n.a.	-	1 (1%)	1 (<1%)

Source: Summary of Clinical Safety adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1
 BW-body weight; PT-preferred term, PY- patient-years; SOC-system organ class, *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits; †-events are in one patient

All Exposure Population

Table 41 provides a summary of all non-fatal SAEs in study WA19977 which includes events in Part I, Part II, and Part III as of May 03, 2012. The most common SAEs were in the SOC Infections and Infestation, consistent with the immunosuppressive effect of tocilizumab. While the incidence of SAEs and serious infections (3 vs. 2) remained numerically higher in the high dose (10 mg/kg) group of patients with body weight <30 kg compared with the low dose (8 mg/kg), the numbers of events (SAEs 4 vs. 3 and serious infections 3 vs. 2) are small to make any definitive conclusions regarding the relative safety of the different dosing regimens, the patients with body weight <30 kg. Further discussion on the exposure-response analyses for safety is provided in section 7.5.1 Dose Dependency for Adverse Events and Analysis of Clinical Information Relevant to Dosing Recommendations.

Table 41. Summary of Non-Fatal Serious AEs in Study WA19977, All Exposure Population as of May 03, 2012 (120-Day Safety Update)

Summary of Non-Fatal Serious AEs in Study WA19977, All Exposure Population as of May 03, 2012					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
No. of patients with ≥ 1 SAE, n (%)	4 (17%)	1 (8%)	3 (9%)	14 (12%)	22 (12%)
Total No. of events SAEs, n (rate per 100 PY)	4 (14)	1 (5)	3 (8)	20 (12)	28 (11)
Event by SOC and PT, n (rate per 100 PY)					
Infection and Infestation	3 (10.6)	1 (5.4)	2 (5.2)	6 (3.5)	12 (4.7)
<i>Pneumonia</i>	1 (3.5)	-	-	3 (1.8)	4 (1.6)
<i>Bronchitis</i>	2 (7.1)	-	-	-	2 (0.8)
<i>Cellulitis</i>	-	-	-	2 (1.2)	2 (0.8)
<i>Epstein-Barr virus infection</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Pyelonephritis</i>	-	1 (5.4)	-	-	1 (0.4)
<i>Varicella</i>	-	-	1 (2.6)	-	1 (0.4)
<i>Viral infection</i>	-	-	1 (2.6)	-	1 (0.4)
Injury, Poisoning, Procedural	-	-	-	3 (1.8)	3 (1.2)
<i>Neck injury</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Synovial rupture</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Upper limb fracture</i>	-	-	-	1 (0.6)	1 (0.4)
Musculoskeletal/Connective Tissue	1 (3.5)	-	-	2 [†] (1.2)	3 (1.2)
<i>Back pain</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Osteoporosis</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Scleroderma</i>	1 (3.5)	-	-	-	1 (0.4)
Congenital, familial, genetic (FMF)	-	-	-	2 [†] (1.2)	2 [†] (0.8)
<i>Familial Mediterranean fever</i>	-	-	-	2 (1.2)	2 (0.8)
Hepatobiliary	-	-	-	2 [†] (1.2)	2 [†] (0.8)
<i>Cholangitis sclerosing</i>	-	-	-	1 (0.6)	1 (0.4)
<i>Hypertransaminasemia</i>	-	-	-	1 (0.6)	1 (0.4)
Eye Disorders	-	-	-	1 (0.6)	1 (0.4)
<i>Uveitis</i>	-	-	-	1 (0.6)	1 (0.4)
Gastrointestinal Disorders	-	-	-	1 (0.6)	1 (0.4)
<i>Constipation</i>	-	-	-	1 (0.6)	1 (0.4)
Nervous System Disorders	-	-	-	1 (0.6)	1 (0.4)
<i>Benign intracranial hypertension</i>	-	-	-	1 (0.6)	1 (0.4)
Respiratory/Thoracic/Mediastinal	-	-	-	1 (0.6)	1 (0.4)
<i>Asthmatic crisis</i>	-	-	-	1 (0.6)	1 (0.4)
Renal/Urinary tract	-	-	-	1 (0.6)	1 (0.4)
<i>Calculus urinary</i>	-	-	-	1 (0.6)	1 (0.4)
Psychiatric Disorders	-	-	-	1 (0.6)	1 (0.4)
<i>Psychosomatic disease</i>	-	-	-	1 (0.6)	1 (0.4)

Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otr_npbo_se_p123a, staerate02_otr_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otr_npbo_se_aewd_p123a, staerate02_otr_npbo_se_aewd_p123a, stae11_s_1
BW-body weight; PT-preferred term; PY- patient-years; SOC-system organ class, *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits; †-events are in one patient

Further details on the individual cases are summarized in Table 42.

Table 42. Listing of SAEs in Study WA19977, as of May 03, 2012

Listing of SAEs in Study WA19977, as of May 03, 2012								
Subject ID		Age/ Sex	Sex	Day of onset	Duration, days	Outcome	Dose adjusted	Discontinued
TCZ 10 mg/kg (<30 kg)								
165103/2062	Bronchitis	4	F	36	8	Resolved	No	No
165122/2091	Pneumonia	7	F	223	14	Resolved	Yes	No
165933/2445	Bronchitis	2	F	20	7	Resolved	No	No
165420/2252	Scleroderma	10	F	649	?	Unresolved	N.A.	Yes
TCZ 10 to 8 mg/kg (<30 kg)								
165652/2552	Pyelonephritis	6	F	564	14	Resolved	No	No
TCZ 8 mg/kg (<30 kg)								
165454/2333	Viral infection	11	M	375	5	Resolved	No	No
165780/2563	Varicella	8	F	303	11	Resolved	Yes	No
165934/2456	Uveitis, left	4	F	239	?	Unresolved	No	No
	Uveitis, right			346	?	Unresolved	No	No
TCZ 8 mg/kg (≥30 kg)								
164946/2004	Constipation	11	F	56	5	Resolved	No	No
	Psychosomatic			117	?	?	No	No
	Osteoporosis			301	?	?	No	No
	Back pain			456	29	Resolved	No	No
164965/2031	Arm fracture	11	F	243	45	Resolved	No	No
165224/2101	Neck injury	11	F	304	90	Resolved	No	No
165246/2495	Pneumonia	10	M	97	11	Resolved	No	No
	FMF			323	2	Resolved	No	No
	FMF			367	4	Resolved	No	No
165453/2321	Cellulitis	13	M	625	11	Resolved	No	No
165655/2521	Pneumonia	11	F	411	11	Resolved	No	No
165780/2562	Cellulitis	10	M	104	12	Resolved	No	No
165782/2581	Calculus urinary	10	F	155	2	Resolved	No	No
165782/2583	Cholangitis	11	M	6	?	Unresolved	N.A.	Yes
	Hypertransaminasemia			6	?	Unresolved	N.A.	Yes
165936/2461	Synovial rupture	12	M	303	13	Resolved	No	No
166138/2624	Benign intracranial hypertension	14	F	6	?	Unresolved	N.A.	Yes
165246/2492	Asthmatic crisis	8	F	704	4	Resolved	No	No
165398/2221	EBV infection	16	M	640	36	Resolved	Yes	No
166181/2651	Pneumonia	6	F	282	35	Resolved	Yes	No
Placebo								
165224/2103	Complicated migraine	13	M	247	4	Resolved	No	No
165936/2465	Enterocolitis	9	M	234	7	Resolved	No	No

Source: CSR WA19977 and 120-days safety update, adapted from table slae01 sall ae; slae01 sall

7.3.3 Dropouts and/or Discontinuations

Adverse events leading to treatment withdrawal/discontinuation in study WA19977 are summarized in Table 43. One patient was withdrawn from the study due to gastroenteritis; however the case is not included in the table as it occurred in a patient randomized to placebo for 157 days (Day 269 in study) and the event was not considered related to tocilizumab exposure based on my review of the case. Of note, one withdrawal was coded by sponsor as juvenile arthritis in the low dose group (8 mg/kg) in the low weight patients; based on the review of the case it represents activity of the underlying disorder, i.e. flare of pJIA. With this caveat, the proportion and incidence rate of AEs leading to study discontinuation were comparable between the 10 mg/kg and 8 mg/kg dose groups in patients <30 kg. Overall, the rates and types of the AEs leading to discontinuation are consistent with the clinical experience with tocilizumab and the underlying disease.

Table 43. Summary of Adverse Events Leading to Treatment Withdrawal in Study WA19977, All Exposure Population

Summary of Adverse Events Leading to Treatment Withdrawal in Study WA19977, All Exposure Population					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
AEs leading to withdrawal, n (rate per 100 PY)	2 (7.1)	-	2 (5.3)	3 (1.8)	7 (2.7)
Scleroderma†	1 (3.5)	-	-	-	1 (0.4)
Hypertransaminasemia†	-	-	-	1 (0.6)	1 (0.4)
Serum sickness-like reaction	-	-	1 (2.6)	-	1 (0.4)
Pneumonia	-	-	-	1 (0.6)	1 (0.4)
Blood bilirubin abnormal	1 (3.5)	-	-	-	1 (0.4)
Juvenile arthritis	-	-	1 (2.6)	-	1 (0.4)
Benign intracranial hypertension†	-	-	-	1 (0.6)	1 (0.4)

Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1
 BW-body weight; PY- patient-years; *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits; †-SAEs

7.3.4 Significant Adverse Events

Adverse events of interest identified in the adult RA population included infections and serious infections, opportunistic infections, tuberculosis, malignancies, gastrointestinal perforations, hypersensitivity reactions and anaphylaxis, and selected laboratory

abnormalities such as hematologic, lipid and liver test abnormalities. The pJIA development program prospectively assessed for these AEs and the findings are summarized in this section.

Infections AEs

Consistent with the mechanism of action of tocilizumab as an immunosuppressant, infections were the most common AEs. As of the 120-day safety update, about 70% of patients reported AEs in the SOC Infections and Infestations with majority of patients reporting less than 5 infections. One 9-year-old female patient treated with tocilizumab 8 mg/kg dose experienced 11 infections of the upper respiratory tract and ears, all of which were mild or moderate in severity and resolved without sequelae.

The most frequent AEs in the SOC Infections and Infestations were nasopharyngitis (rate about 27 events per 100 patient years, versus 30 events/100 PY in the original submission) and upper respiratory tract infections (rate of 17 events/100 PY compared with 20 events/100 PY in the original submission).

The incidence of exposure-adjusted rates of infections over time is summarized in Table 44. Analysis of the data shows relatively lower incidence with short-term compared with longer term exposure to tocilizumab, suggesting a lagging period of the clinical immunosuppression relative to the initiation of tocilizumab. However the overall incidence of infections remained stable with prolonged exposure between the original submission and the 120-day safety update. The overall incidence of infections was comparable across the different dosing regimens with no clear dose-dependent differences over time. Further, most of the reported infections were mild to moderate in intensity and resolved without sequelae. There was no clear association between infections and decreased neutrophil counts as discussed in section 7.4.2.1 Hematology Parameters.

The overall pattern and incidence of infections are as expected for the study population and are consistent with the rates seen in adult RA as discussed in section 7.6
Additional Safety Evaluations

Table 44. Summary of AEs in SOC Infections and Infestation Over Time in Study WA19977

Summary of AEs in SOC Infections and Infestation Over Time in Study WA19977					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
No. of patients with ≥ 1 AE, n (%)	21 (91%)	10 (83%)	29 (85%)	107 (90%)	167 (89%)
Total No. of AEs, n (rate per 100 PY)	113 (399)	60 (321)	180 (471)	778 (458)	1131 (443)
AEs in SOC Infections and Infestation, n (rate per 100 PY)					
Part I, Weeks 0-16	17 (155)	n.a.	11 (110)	50 (135)	78 (134)
All Exposure as of November 04, 2011	49 (199)	6** (69)	48 (177)	199 (161)	302 (164)
All Exposure as of May 03, 2012	51 (180)	21 (112)	79 (204)	263 (154)	413 (162)
Source: CSR WA19977 and 120-day safety update, adapted from tables staerate02_ortr_npbo_se_p123a					
*In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits, **as of November 04, 2011 only 7 patients met criteria to have their dose changed to 8 mg/kg					

Serious infections

A total of 12 SAEs were reported in the SOC Infections and Infestations as shown in Table 41 above. While the exposure-adjusted incidence of SAEs is numerically higher in the 10 mg/kg dose group compared with the 8 mg/kg group in the patients with body weight of less than 30 kg, the numbers are small making definitive conclusions on the dose-relatedness difficult. Further, the types of serious infections are characteristic for the study population. The rates of serious infections overall infections are numerically higher in the smaller patients compared with heavier patients. This observations is consistent with the findings in other pediatric development programs likely reflecting the fact that younger patients are more prone to common pediatric infections compared with older children.

Tuberculosis

All patients were screened for latent TB infection at baseline and Week 52 per protocol. Nine PPD-positive patients at baseline received prophylactic treatment per local guidelines and continued tocilizumab treatment. Among the patients who had reached Week 52, 19 tested PPD positive, of whom 10 converted from baseline as shown in Table 45 and nine received prophylaxis for latent TB infection. One of the 10 patients, (patient 2651) from Peru, who immuno-converted from baseline was diagnosed with primary TB based on X-ray findings and was treated with isoniazid.

In summary, no cases of TB reactivation were reported and one patient from endemic area developed primary pulmonary TB in study WA19977 and the supporting Japanese studies MRA318/319JP.

Table 45. Summary of Patients with Positive PPD Skin Test in Study WA19977

Summary of Patients with Positive PPD Skin Test in Study WA19977					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
AEs in SOC Infections and Infestation, n (%)					
Baseline PPD positive	2 (9%)	1 (8%)	2 (6%)	4 (3%)	9 (5%)
Week 52 PPD positive	3 (13%)	1 (8%)	4 (12%)	11 (9%)	19 (11%)
Conversion from baseline	1 (4%)	-	2 (6%)	7 (6%)	10 (5%)
Source: CSR WA19977 and 120-day safety update, adapted from Tables 12					
*In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits.					

Opportunistic infections

No opportunistic infections were reported in study WA19977 and the supporting Japanese studies MRA318/319JP.

Malignancies

No malignancies were reported in study WA19977 and the supporting Japanese studies MRA318/319JP. While reassuring, the lack of reported malignancies should be interpreted in the context of the relatively small overall extent and duration of exposure in the safety database in this program.

Gastrointestinal perforations

There were no events of gastrointestinal perforations reported in study WA19977 and the supporting Japanese studies MRA318/319JP. In the post-marketing setting, one case of a perforated gastric antral ulcer was reported; the case was confounded by concomitant ibuprofen use which is consistent with the increased risk of gastrointestinal perforations in adult RA patients treated with concomitant NSAIDs or corticosteroids.

Hypersensitivity and anaphylaxis

Anaphylaxis, including fatal one has been observed in the adult RA development. In pJIA development however, no cases of hypersensitivity or anaphylaxis (defined by Sampson's criteria³) were reported in study WA19977 and the supporting Japanese studies MRA318/319JP. In addition, no events with the preferred term of hypersensitivity were reported during the study. There were two patients, each in study WA19977 and MRA319JP who tested positive for neutralizing anti-tocilizumab antibodies; however this was not associated with hypersensitivity, anaphylaxis, or clinically significant infusion reactions.

Infusion AEs

Infusion reactions were defined as any AE occurring during an infusion or within 24 hours of infusion. The incidence of infusions reactions occurring during the infusion and within 24 hours of infusions are summarized in Table 46. The incidence of infusion-related reactions during infusion was rare and proportional across the treatment arms. The most common infusion AE terms occurring during infusion were hypotension, nausea, and headache, all occurring at similar rates of 2 events per 100 patient years of exposure. The most common infusion AE terms occurring within 24 hours after an infusion were dizziness, hypotension, nausea, and pyrexia. No specific treatments were given for the cases of hypotension and all events resolved without sequelae.

Table 46. Summary of Infusion Reactions in Study WA19977, All Exposure Population, as of May 03, 2012

Summary of Infusion Reactions in Study WA19977, All Exposure Population, as of May 03, 2012					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
All Exposure Population As of 11/04/2011 (Original submission)					
Enrolled, n	28	7	34	119	188
TCZ Exposure, PY	23	9	25	120	177
Duration in study, PY	25	9	27	124	184
Events within 24 hours after infusion					
Number of patients with ≥ 1 event, n (%)	2 (7%)	2 (29%)	5 (15%)	29 (24%)	38 (20%)
Number of events, n (rate per 100 PY)	4 (16)	2 (23)	5 (18)	44 (36)	55 (30)
Events during infusion					
Number of patients with ≥ 1 event, n (%)	1 (3%)	1 (14%)	3 (9%)	6 (5%)	11 (6%)
Number of events, n (rate per 100 PY)	1 (4)	1 (23)	3 (11)	8 (7)	14 (8)

Source: CSR WA19977 and 120-day safety update, adapted from tables staerate02_otrt_npbo_se_inf2_p123a; staerate02_otrt_npbo_se_inf2_p123a; staerate02_otrt_npbo_se_inf3_p123a

Demyelinating disorders

3 Sampson HA, et al. Second symposium on the definition of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. JACI 2006;117(2):391-7

There were no events of confirmed or potential demyelinating disorders reported in study WA19977 or in the supporting Japanese studies MRA318/319JP.

Laboratory abnormalities

The findings of laboratory abnormalities and associated AEs are discussed in section 7.4.2 Laboratory Findings.

7.3.5 Submission Specific Primary Safety Concerns

For discussion on primary safety concerns see section 1.2 Risk Benefit Assessment.

7.4 Supportive Safety Results

Safety data from the supportive Japanese studies MRA318/319JP did not identify a new safety signal and were consistent with the findings from the registration trial WA19977. These findings are summarized below:

Studies MRA318JP and MRA319JP

This was an open-label study conducted at five sites in Japan between November 2004 and July 2005. Patients were given three TCZ infusions of 8 mg/kg at 4-week intervals. The last observations were made at the week 12 visit, 4 weeks after the last infusion. The dose regimen and duration of treatment were based on the TCZ dosage regimen for RA in adults. In contrast to study WA19977, concomitant treatment with any DMARDs, including MTX, was not permitted. The study enrolled a total of 19 patients 2 to 19 years of age who had been under 16 years of age at disease onset. Patients had to have a diagnosis of RF-positive or RF-negative polyarticular JIA or oligoarticular JIA according to the ILAR criteria.

Study MRA319JP was the long-term extension of study MRA318JP. The primary objective was to investigate the safety, efficacy, and pharmacokinetics of long-term treatment with TCZ for pJIA. Patients continued to receive open-label TCZ at a dose of 8 mg/kg q4w for at least one year after the first infusion in MRA318JP.

The following summarizes the safety findings in studies MRA318JP and MRA319JP:

- There were no deaths
- No cases of anaphylaxis were reported
- No cases of gastrointestinal perforation were reported
- No Hy's law cases were reported
- Four of the 19 patients were withdrawn from the study:
 - one due to an AE (myasthenia gravis),
 - one due to development of anti-TCZ antibodies before the 4th infusion without associated AEs or loss of efficacy

- 2 due to insufficient therapeutic response
- There were six SAEs in 4 patients: 2 SAEs of gastroenteritis and one sensory disturbance, influenza, pneumonia, and myasthenia gravis
- 11/19 patients (57.9%) had infections and infestations
- Those with an incidence of 10% or higher were upper respiratory tract infections (5 events) and nasopharyngitis (4 events)
- Infections and infestations were the most common AEs: 60 events in 18/19 patients (94.7%)
- Gastrointestinal disorders: 18 events in 12/19 patients (63.2%)
- Skin and subcutaneous tissue disorders: 14 events in 12/19 patients (63.2%)
- Injuries, poisoning, and procedural complications: 16 events in 10/19 patients (52.6%)
- Respiratory, thoracic and mediastinal disorders: 6 events in 6/19 patients (31.6%)
- 2 infusion reactions (10%)
- Laboratory abnormalities were consistent with the findings in study WA19977.

7.4.1 Common Adverse Events

Overall, the types and the incidence of the common AEs, defined as AEs occurring in ≥ 5 % of patients in any group, are consistent with the previous experience with tocilizumab and the underlying patient population as summarized in Table 47.

Table 47. Common Adverse Events (Incidence \geq 5%) by Preferred Term in Study WA19977, All Exposure Population

Common AEs (Incidence \geq 5%) by PT in Study WA19977, All Exposure Population, as of November 04, 2011					
	BW <30 kg			BW \geq 30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	28	7*	34	119	188
TCZ Exposure, PY	23	9	25	120	177
Duration in study, PY	25	9	27	124	184
PT term, No. of patients (%)					
Juvenile arthritis	6 (21)	2 (29)	6 (18)	35 (29)	49 (26)
Nasopharyngitis	6 (21)	-	5 (15)	28 (24)	39 (21)
Headache	3 (11)	-	5 (15)	18 (15)	26 (14)
Upper respiratory tract infection	2 (7)	-	3 (9)	14 (12)	19 (10)
Cough	2 (7)	2 (29)	3 (9)	11 (9)	18 (10)
Pharyngitis	3 (11)	-	2 (6)	12 (10)	17 (9)
Nausea	-	-	2 (6)	14 (12)	16 (9)
Diarrhea	1 (4)	-	2 (6)	11 (9)	14 (7)
Rhinitis	2 (7)	1 (14)	4 (12)	7 (6)	14 (7)
Vomiting	1 (4)	1 (14)	3 (9)	9 (8)	14 (7)
Abdominal pain	1 (4)	1 (14)	2 (6)	9 (8)	13 (7)
Oropharyngeal pain	1 (4)	-	2 (6)	10 (8)	13 (7)
Rash	1 (4)	-	3 (9)	6 (5)	10 (5)

Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1; stae13_ae
 BW-body weight; PY- patient-years; SOC-system organ class, *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to \geq 30 kg and at least 5 kg over baseline weight for 3 consecutive visits

Part I

AEs during the open-label lead-in period, Part I are reviewed separately from the all exposure population, to allow for the least confounded head-to-head comparisons across the treatment regimens. As shown in Table 48 during the first 16 weeks of tocilizumab treatment higher proportion of patients in the 10 mg/kg dose group (77%) experienced an AE and infections (49%) as compared with the other treatment groups, and specifically with the 8 mg/kg group of patients <30 kg. This is similar to the observations of SAEs and serious infections indicating exposure-dependent immunosuppression in patients with body weight <30 kg.

Table 48. Summary of Adverse Events by SOC at Week 16, by Dosing Regimen, Study WA19977

Summary of AEs by SOC at Week 16, by Dosing Regimen, Study WA19977				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled	35	34	119	188
No. of AEs, n	53	56	223	332
No. of patients with ≥1 AE, n (%)	27 (77%)	22 (65%)	75 (63%)	124 (66%)
SOC Event, No. of patients (%)				
Infection and Infestation	17 (49%)	11 (32%)	50 (42%)	78 (42%)
Gastrointestinal Disorders	5 (14%)	6 (18%)	30 (25%)	41 (22%)
Nervous System Disorders	1 (3%)	6 (18%)	18 (15%)	25 (13%)
Respiratory/Thoracic/Mediastinal	5 (14%)	4 (12%)	12 (10%)	21 (11%)
Respiratory/Thoracic/Mediastinal	1 (3%)	3 (10%)	16 (13%)	20 (11%)
Musculoskeletal/Connective Tissue	4 (11%)	4 (11%)	11 (9%)	19 (10%)
Injury, Poisoning, Procedural	3 (9%)	2 (6%)	7 (6%)	12 (6%)
General and Admin Site	1 (3%)	1 (3%)	9 (8%)	11 (6%)
Eye Disorders	1 (3%)	4 (12%)	3 (3%)	8 (4%)
Vascular Disorders	1 (3%)	1 (3%)	4 (3%)	6 (3%)
Reproductive/Breast	1 (3%)	2 (6%)	2 (2%)	5 (3%)
Immune System	1 (3%)	1 (3%)	2 (6%)	4 (2%)
Investigations	2 (6%)	-	2 (2%)	4 (2%)
Blood and Lymphatic	-	-	3 (3%)	3 (2%)
Renal/Urinary tract	-	1 (3%)	2 (2%)	3 (2%)
Ear and Labyrinth	-	-	2 (2%)	2 (1%)
Hepatobiliary	-	-	1 (1%)	1 (<1%)
Metabolism/Nutrition	-	-	1 (1%)	1 (<1%)
Cardiac Disorders	-	-	1 (1%)	1 (<1%)
Psychiatric Disorders	-	1 (3%)	-	1 (<1%)

Source: CSR WA19977, adapted from Table stae11_1

Part II

AEs for the randomized withdrawal period, Part II, are reviewed by treatment group for completeness and summarized in Table 49. The numerical differences suggest that patients with body weight less than 30 kg treated with the 8 mg/kg dose of TCZ had a higher exposure-adjusted rates of AEs, mostly driven by the AEs in SOC Infections and infestation, Gastrointestinal disorder, Respiratory/thoracic/mediastinal disorders, and Skin and subcutaneous disorders. However definitive conclusions regarding the relative safety among the treatment groups cannot be made because of the following study design limitations:

- All patients were previously treated with TCZ in Part I and continued to have TCZ exposure (circulating systemic TCZ) even after withdrawal to placebo, therefore AE attribution to placebo or TCZ cannot be ascertained.
- Patients randomized to placebo withdrawal had higher incidence of JIA flares and were re-started on TCZ at variable time points during Part II leading to variable and generally lower cumulative exposure in the placebo-withdrawal group compared with TCZ-treated group
- Further, the TCZ-treated group had a continuous exposure to TCZ in contrast to placebo-withdrawal group. To account for the differences in exposure, the sponsor has presented the incidence of the AEs adjusted for the exposure for that period as events per 100 patient-years, consistent with the safety data presentation in the submission.

Table 49. Summary of AEs by SOC in Part II, by Dosing Regimen, Study WA19977

Summary of AEs by SOC in Part II, by Dosing Regimen, Study WA19977						
	TCZ (N=82)			Placebo (N=84)		
	BW <30 kg		BW ≥30 kg	BW <30 kg		BW ≥30 kg
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg
Randomized and treated, ITT	16	11	55	15	13	53**
Completed Part II, n (%)	15 (94)	11 (100)	52 (95)	15 (100)	13 (100)	52 (98)
Duration in study, PY	6.9	4.4	20.9	5.2	4.7	17.6
No. of patients with ≥ 1 AE, n (%)	9 (56%)	8 (73%)	41 (75%)	9 (60%)	12 (92%)	39 (74%)
Total No. of AEs, n (rate per 100 PY)	19 (274)	21 (473)	107 (511)	21 (405)	31 (665)	89 (507)
Event by SOC, n (rate per 100 PY)						
Infection and Infestation	10 (144)	9 (203)	37 (177)	5 (96)	10 (214)	28 (160)
Musculoskeletal/Connective Tissue	-	-	12 (57)	6 (116)	5 (107)	17 (97)
Gastrointestinal Disorders	1 (14)	1 (23)	20 (96)	3 (58)	6 (129)	13 (74)
Respiratory/Thoracic/Mediastinal	1 (14)	2 (45)	6 (29)	2 (39)	3 (64)	7 (40)
Skin and Subcutaneous	2 (29)	4 (90)	7 (33)	2 (39)	1 (21)	4 (23)
Injury, Poisoning, Procedural	3 (43)	1 (23)	5 (24)	-	1 (21)	6 (34)
Investigations	1 (14)	-	3 (14)	1 (19)	1 (21)	1 (6)
Eye Disorders	-	-	2 (10)	-	2 (43)	4 (23)
General and Admin Site	1 (14)	2 (45)	2 (10)	1 (19)	-	1 (6)
Nervous System Disorders	-	1 (23)	6 (29)	-	1 (21)	2 (11)
Psychiatric Disorders	-	-	1 (5)	-	1 (21)	1 (6)
Blood and Lymphatic	-	-	1 (5)	1 (19)	-	-
Ear and Labyrinth	-	1 (23)	-	-	-	1 (6)
Immune System	-	-	-	-	-	2 (11)
Metabolism/Nutrition	-	-	2 (10)	-	-	-
Neoplasms, benign, malignant	-	-	2 (10)	-	-	-
Renal/Urinary tract	-	-	-	-	-	1 (6)
Reproductive/Breast	-	-	-	-	-	1 (6)
Surgical and medical procedures	-	-	1 (5)	-	-	-

Source: CSR WA19977, adapted from Tables 45 and staerate02_otr_nesc_se2_p2
BW-body weight
* Patient 2583 missed the Week 16 infusion, completed Week 18 and then withdrew at the next visit; Patients 2122 and 2682 withdrew while receiving Part II escape medication.
** A total of 56 patients were randomized but three patients received no infusion in Part II and were not included in the ITT population (table stec11_rnd_a_2)

All Exposure Population

The overall trends of AEs and infections with respect to dosing regimen however, were not sustained with prolonged tocilizumab exposure as assessed by the analysis of AEs

in the all exposure population shown in Table 50 which may be due to confounders such as differences in continuous exposure, drop outs, and increase in the cumulative tocilizumab exposure across all groups. Majority of the AEs were mild and moderate in severity. Serious AEs and AEs leading to withdrawal or dose interruptions are discussed in the related sections elsewhere in this review.

Table 50. Summary of AEs by SOC in Study WA19977, All Exposure Population, as of May 03, 2012

Summary of AEs by SOC in Study WA19977, All Exposure Population, as of May 03, 2012					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg*	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
TCZ Exposure, PY	28	19	38	172	257
Duration in study, PY	29	19	38	170	255
No. of patients with ≥ 1 AE, n (%)	21 (91%)	10 (83%)	29 (85%)	107 (90%)	167 (89%)
Total No. of AEs, n (rate per 100 PY)	113 (399)	60 (321)	180 (471)	778 (458)	1131 (443)
Event by SOC, n (rate per 100 PY)					
Infection and Infestation	51 (180)	21 (112)	79 (204)	263 (154)	413 (162)
Musculoskeletal/Connective Tissue	14 (49)	9 (48)	7 (18)	80 (47)	110 (43)
Gastrointestinal Disorders	6 (21)	4 (21)	21 (55)	118 (69)	149 (58)
Respiratory/Thoracic/Mediastinal	12 (42)	8 (43)	15 (39)	56 (33)	91 (36)
Skin and Subcutaneous	6 (21)	2 (11)	16 (42)	49 (29)	73 (29)
Injury, Poisoning, Procedural	11 (39)	4 (21)	8 (21)	34 (20)	57 (22)
Nervous System Disorders	3 (11)	3 (16)	8 (21)	57 (34)	71 (28)
General and Admin Site	3 (11)	1 (5)	5 (13)	19 (11)	28 (11)
Eye Disorders	2 (7)	-	5 (13)	12 (7)	19 (7)
Blood and Lymphatic	-	5 (27)	4 (10)	14 (8)	23 (9)
Investigations	4 (14)	-	2 (5)	13 (8)	19 (7)
Ear and Labyrinth	-	-	2 (5)	8 (5)	10 (4)
Reproductive/Breast	-	1 (5)	3 (8)	6 (4)	10 (4)
Vascular Disorders	-	2 (11)	1 (3)	6 (4)	9 (4)
Immune System	1 (4)	-	1 (3)	6 (4)	8 (3)
Neoplasms, benign, malignant	-	-	-	9 (5)	9 (4)
Renal/Urinary tract	-	-	1 (3)	6 (4)	7 (3)
Metabolism/Nutrition	-	-	2 (5)	6 (4)	8 (3)
Psychiatric Disorders	-	-	1 (3)	3 (2)	4 (2)
Surgical and medical procedures	-	-	-	4 (2)	4 (2)
Hepatobiliary	-	-	-	4 (2)	4 (2)
Cardiac Disorders	-	-	-	1 (<)	1 (<1)
Congenital, familial, genetic	-	-	-	1 (<)	1 (<1)
Endocrine disorders	-	-	-	1 (<)	1 (<1)

Source: Summary of Clinical Safety, and 120-Day Safety Update, adapted from Tables std1_durexp_ae, stdm11_durexp; staerate02_otrt_npbo_se_p123a, staerate02_otrt_npbo_se_ser_p123a, stae11_dm, stae11, staerate02_otrt_npbo_se_aewd_p123a, staerate02_otrt_npbo_se_aewd_p123a, stae11_s_1; stae13_ae
 BW-body weight; PY- patient-years; SOC-system organ class, *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits

7.4.2 Laboratory Findings

Summary of Laboratory Findings and Conclusions

As previously reported, TCZ treatment resulted in dose-dependent changes of certain hematology, hepatobiliary and lipid parameters. Overall, the neutrophil and platelet counts remained within the normal range. TCZ treatment resulted in relatively small increases of the liver enzymes. Importantly, the increases seen in the total bilirubin were largely due to increases in unconjugated and not in direct bilirubin. Dyslipidemia also developed after TCZ initiation. The small increases were seen in all lipid parameters, including HDL.

The reported laboratory changes in pJIA development program were consistent with the ones seen in the RA and sJIA populations. No clear exposure-dependence (8 mg/kg vs. 10 mg/kg TCZ dose) in laboratory abnormalities with respect to the patients with body weight < 30 kg was observed.

No new laboratory abnormalities were reported in this submission to indicate a new clear safety signal.

7.4.2.1 Hematology Parameters

Neutrophil counts

The mean absolute neutrophil counts have remained within normal range. With regard to neutrophil shifts from baseline, majority of the patients maintained normal neutrophil counts with only a small proportion of patients experiencing single occurrences of neutropenia meeting the CTCAE Grade 3 (eight patients) or Grade 4 (no cases) as shown in Table 51. These observations are consistent with the experience in adult RA population. The observed shifts in neutrophil counts were not generally associated with clinically significant events of infections; only two of the patients with Grade 3 or 4 experienced coincident infections (one gastroenteritis in patient 2496, TCZ 8 mg/kg, \geq 30 kg, and one tracheitis in Patient 2611, TCZ 10 mg/kg, < 30 kg). There were no AEs of neutropenia (based on sponsor's pre-defined criteria) reported during the study. Importantly, the head-to-head relative comparison of the incidence of Grade 3 and 4 neutropenia during the lead-in period, Part I, did not reveal any dose-dependence.

In the supporting Japanese studies MRA318JP and MRA319JP mean neutrophil counts decreased by about 30% but remained within normal limits throughout the studies. A single patient was reported to have experienced AE of neutropenia Grade 3 without associated infections.

Platelet counts

Similarly to adult RA patients, treatment with TCZ resulted in comparable decreases in mean platelet counts across all treatment groups possibly reflecting an effect of TCZ on reducing the systemic inflammation rather than off-target toxicity. Further, these decreases were generally CTCAE Grade 1 or 2 with only single patients experiencing Grades 3 and 4 as shown in Table 51. The observed thrombocytopenia was not associated with bleeding AEs with the exception of one case of pre-menstrual spotting in a patient with platelet counts of $114 \times 10^9/L$. Two cases of MedDRA thrombocytopenia SMQ (standardized MedDRA query) were identified; both were mild, transient and non-serious, and were not associated with bleeding events.

Similar degree of decreases in mean platelet counts were observed in the supporting Japanese studies MRA318JP and MRA319/JP and no AEs of thrombocytopenia were reported.

Other Hematology Parameters

No patients experienced a worsening in white blood cell counts or lymphocyte counts of CTCAE Grade 3 or 4 and only a single patient experienced a Grade 3 worsening of hemoglobin. The observed abnormalities did not suggest a dose-dependence with regard to the 8mg/kg and 10 mg/kg dose in patients with body weight <30 kg.

Overall, the observed hematologic abnormalities in pJIA are consistent with the experience in the RA and sJIA populations and were not clearly associated with clinically significant adverse events.

Table 51. Worst CTC Grades for Hematologic Laboratory Parameters in Study WA19977, All Exposure Population

Worst CTC Grades for Hematologic Laboratory Parameters in Study WA19977, All Exposure Population					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n (%)	23	12*	34	119	188
White blood cells					
Normal	9 (39%)	5 (42%)	20 (59%)	52 (44%)	86 (46%)
Grade 1	14 (61%)	7 (58%)	12 (35%)	59 (50%)	92 (49%)
Grade 2	-	-	2 (6%)	8 (7%)	10 (5%)
Grade 3	-	-	-	-	-
Grade 4	-	-	-	-	-
Neutrophils					
Normal	17 (74%)	8 (77%)	24 (71%)	70 (59%)	119 (63%)
Grade 1	-	1 (8%)	-	15 (13%)	16 (9%)
Grade 2	4 (17%)	3 (25%)	7 (21%)	31 (26%)	45 (24%)
Grade 3	2 (9%)	-	3 (9%)	3 (3%)	8 (4%)
Grade 4	-	-	-	-	-
Lymphocytes					
Normal	17 (74%)	10 (83%)	30 (88%)	106 (89%)	163 (87%)
Grade 1	5 (22%)	2 (17%)	4 (12%)	8 (7%)	19 (10%)
Grade 2	1 (4%)	-	-	5 (4%)	6 (3%)
Grade 3	-	-	-	-	-
Grade 4	-	-	-	-	-
Platelets					
Normal	18 (78%)	11 (92%)	32 (94%)	108 (91%)	169 (90%)
Grade 1	4 (17%)	1 (8%)	2 (6%)	9 (8%)	16 (9%)
Grade 2	-	-	-	1 (1%)	1 (<1%)
Grade 3	1 (4%)	-	-	-	1 (<1%)
Grade 4	-	-	-	1 (1%)	1 (<1%)
Hemoglobin					
Normal	10 (44%)	7 (58%)	23 (78%)	71 (60%)	111 (59%)
Grade 1	9 (39%)	4 (33%)	10 (29%)	42 (35%)	65 (35%)
Grade 2	3 (13%)	1 (8%)	1 (3%)	6 (5%)	11 (6%)
Grade 3	1 (4%)	-	-	-	1 (<1%)
Grade 4	-	-	-	-	-

Source: CSR WA19977 and 120-day safety update, adapted from Tables stswfrq01_cgp2_se_sw123_xpbo; stdm11_elv_n4c; stswfrq01_cgp2_se_sw123_xpbo;
BW-body weight; CTC-common toxicology criteria; PY- patient-years; *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits

7.4.2.2 Hepatobiliary Parameters

Liver Test Abnormalities

Similarly with RA and sJIA patients, the pJIA patients in study WA19977 experienced liver test (ALT, AST, and total bilirubin) abnormalities with comparable overall incidence and severity without a clear dose-relatedness. As shown in Table 52, there were no CTCAE Grade 4 abnormalities and only single patients developed Grade 3 abnormalities in ALT, AST or total bilirubin. A total of 10 patients (5.3%) experienced ALT elevation \geq than 3 x ULN without a clear dose-dependency. The patients who experienced this degree of ALT elevations maintained normal bilirubin levels. No cases met the Hy's law criteria to indicate an increased risk of clinically significant hepatotoxicity in this patient population. While reassuring, these data are derived from a relatively small program but appear consistent with the overall hepatobiliary safety profile of TCZ in adult RA.

Table 52. Worst CTC Grades for Hepatobiliary Laboratory Parameters in Study WA19977, All Exposure Population

Worst CTC Grades for Hepatobiliary Laboratory Parameters in Study WA19977, All Exposure Population					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n (%)	23	12*	34	119	188
ALT (SGPT)					
Normal	18 (78%)	7 (58%)	25 (76%)	64 (54%)	114 (61%)
Grade 1	3 (13%)	5 (42%)	5 (15%)	47 (40%)	60 (32%)
Grade 2	2 (9%)	-	2 (6%)	6 (5%)	10 (5%)
Grade 3	-	-	1 (3%)	2 (2%)	3 (2%)
Grade 4	-	-	-	-	-
ALT ≥ 3 x ULN elevation	1 (4%)	-	2 (6%)	7 (6%)	10 (5%)
AST (SGOT)					
Normal	19 (83%)	8 (67%)	27 (82%)	84 (71%)	138 (74%)
Grade 1	3 (13%)	4 (33%)	5 (15%)	31 (26%)	43 (23%)
Grade 2	1 (4%)	-	-	2 (2%)	3 (2%)
Grade 3	-	-	1 (3%)	2 (2%)	3 (2%)
Grade 4	-	-	-	-	-
AST ≥ 3 x ULN elevation	-	-	-	1 (1%)	1 (<1%)
Bilirubin					
Normal	21 (91%)	9 (75%)	30 (91%)	98 (82%)	158 (85%)
Grade 1	-	2 (17%)	3 (9%)	11 (9%)	16 (9%)
Grade 2	2 (9%)	1 (8%)	-	9 (8%)	12 (6%)
Grade 3	-	-	-	1 (1%)	1 (<1%)
Grade 4	-	-	-	-	-
Source: CSR WA19977 and 120-day safety update, adapted from Tables stswfrq01_cgp2_se_sw123_xpbo; stdm11_elv_n4c; stswfrq01_cgp2_se_sw123_xpbo; stswfrq01_cgp1_se_sw123_xpbo; stlbdm11_east; stlbdm11_ealt; BW-body weight; CTC-common toxicology criteria; PY- patient-years; *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits					

Hepatobiliary AEs

Only one serious hepatobiliary AE was reported; patient 165782/2583 treated with TCZ 8 mg/kg, (≥30 kg) who was diagnosed with sclerosing cholangitis unlikely related to TTCZ treatment as the laboratory abnormalities were present on day 6 after enrollment. The patient received treatment for the hypertransaminasemia and was discontinued from the study. One additional case of non-serious transient AE of hepatotoxicity (ALT 88 U/L with normal AST and bilirubin) on Day 342 attributed to concomitant use of

methotrexate was reported in a 16-year-old female patient 165655/2523 treated with TCZ 8 mg/kg, (≥ 30 kg) who continued treatment in the protocol.

No AEs of hepatobiliary disorders SOC were reported in the supporting Japanese studies MRA318JP and MRA319/JP.

Overall, the observed liver test abnormalities in pJIA are consistent with the experience in the RA and sJIA populations and were not associated with increased risk of clinical hepatotoxicity.

7.4.2.3 Lipid Parameters

Mean total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride remained within normal ranges during study WA19977. No patients experienced elevation in either total cholesterol or LDL-cholesterol over 2 x ULN and only single patients developed elevations of higher than 1.5 x ULN as shown in Table 53.

The overall lipid abnormalities are consistent with those observed in the RA and sJIA populations. The clinical significance of these abnormalities remains unclear at this time. To address the possibility of potentially increased cardio-vascular risk of TCZ use, the sponsor is currently conducting a cardio-vascular outcomes study as a post-marketing requirement.

Table 53. Summary of Lipid Parameter Abnormalities During Study WA19977, All Exposure Population

Summary of Lipid Parameter Abnormalities During Study WA19977, All Exposure Population					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n	23	12*	34	119	188
Assessed, n (%)	23	12*	33	117	185
Total cholesterol					
Normal	22 (96%)	12 (100%)	31 (94%)	104 (89%)	169 (91%)
>ULN to 1.5 x ULN	1 (4%)	-	2 (6%)	12 (10%)	15 (8%)
>1.5 x ULN to 2 x ULN	-	-	-	1 (1%)	1 (<1%)
>2 x ULN	-	-	-	-	-
Cholesterol elevation ≥ 170 mg/dL	7 (30%)	1 (8%)	14 (42%)	50 (43%)	72 (39%)
Cholesterol elevation ≥ 200 mg/dL	1 (4%)	-	2 (6%)	14 (12%)	17 (9%)
LDL-cholesterol					
Normal	22 (96%)	12 (100%)	32 (97%)	111 (95%)	177 (96%)
>ULN to 1.5 x ULN	1 (4%)	-	1 (3%)	5 (4%)	7 (4%)
>1.5 x ULN to 2 x ULN	-	-	-	1 (1%)	1 (<1%)
>2 x ULN	-	-	-	-	-
LDL elevation ≥ 110 mg/dL	2 (8%)	-	3 (9%)	20 (17%)	25 (13%)
LDL elevation ≥ 130 mg/dL	1 (4%)	-	1 (3%)	6 (5%)	8 (4%)
HDL-cholesterol					
Assessed, n	17	12	32	117	178
Normal	12 (71%)	10 (83%)	28 (88%)	84 (72%)	134 (75%)
>ULN to 1.5 x ULN	5 (29%)	2 (17%)	4 (12%)	32 (27%)	43 (24%)
>1.5 x ULN to 2 x ULN	-	-	-	1 (1%)	1 (<1%)
>2 x ULN	-	-	-	-	-
Source: CSR WA19977 and 120-day safety update, adapted from Tables stswfrq02_lpd_se_sw123_xpbo; stdm11_elv_cho; stdm11_elv_idc; Per protocol, lipid parameters were assessed at Baseline, Weeks 8, 16, 52, 80, and 104					
BW-body weight; CTC-common toxicology criteria; PY- patient-years; *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits					

7.4.3 Vital Signs

The incidence of the vital signs abnormalities, including systolic blood pressure (SBP), diastolic blood pressure (DBP) and weight changes over 10% from baseline are summarized in Table 54. The observed abnormalities in each category were balanced among the treatment groups and do not indicate a safety concern. Weight increases seen in study WA19977 reflect the physical growth expected for the study population.

Table 54. Summary of Vital Signs Abnormalities During Study WA19977, All Exposure Population

Summary of Vital Signs Abnormalities During Study WA19977, All Exposure Population					
	BW <30 kg			BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 10 to 8 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
Enrolled, n (%)	23	12*	34	119	188
SBP					
High (>ULN and ↑>20 mmHg CFB)	1 (4%)	-	5 (15%)	24 (21%)	30 (16%)
Low (<LLN and ↓>20 mmHg CFB)	8 (35%)	3 (25%)	10 (29%)	65 (48%)	77 (41%)
DBP					
High (>ULN and ↑>20 mmHg CFB)	2 (9%)	2 (17%)	6 (18%)	26 (22%)	36 (19%)
Low (<LLN and ↓>20 mmHg CFB)	9 (39%)	2 (17%)	7 (21%)	34 (29%)	52 (28%)
Weight					
High (↑>10% CFB)	20 (87%)	12 (100%)	23 (68%)	70 (59%)	125 (66%)
Low (↓>10% CFB)	-	-	1 (3%)	4 (3%)	5 (3%)

Source: CSR WA19977 and 120-day safety update, adapted from Table stvsdm11_ab
 BW-body weight; CFB-change from baseline; DBP-diastolic blood pressure; PY- patient-years; SBP-systolic blood pressure; *In Part III only, patients had their TCZ dose decreased to 8 mg/kg if their weight increased to ≥30 kg and at least 5 kg over baseline weight for 3 consecutive visits

7.4.4 Electrocardiograms (ECGs)

Electrocardiographic assessment was performed at screening. No ECG abnormalities were reported in this submission.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted with this supplement.

7.4.6 Immunogenicity

Anti-TCZ antibodies (human anti-human antibody, or HAHA) were assessed on samples taken at baseline and at selected post-baseline visits. Samples positive on the screening assay were analyzed by a confirmation assay. Patients with a positive confirmation assay were tested with the neutralizing assay. In other words, if the screening assay is negative then the confirmatory and neutralizing assays are assumed to be negative. The assays used in this submission were identical to the assays previously used by the sponsor which allows for reasonable comparison of immunogenicity from this supplement and previous submissions.

A summarized in Table 55, almost all patients (187/188, 99.5%) enrolled in study WA19977 were tested with the screening assay. Of these, 20 patients (10.6%) had

positive baseline anti-TCZ assay results, 3 (1.6%) had positive screening assay results post-baseline, and 1 had positive confirmation and neutralizing assay results post-baseline (0.5%). This patient (2343) developed the anti-TCZ neutralizing antibodies at Week 20.

Table 55. Summary of Patients with Anti-TCZ Assay in Study WA19977, All Exposure Population

Summary of Patients with Anti-TCZ Assay in Study WA19977, All Exposure Population		
	n	%
Enrolled	188	100
Tested at any time point	187	99.5
Positive screening anti-TCZ assay, baseline	21	11.1
Positive screening anti-TCZ assay, post-baseline	3	1.6
Positive confirmation anti-TCZ assay	1	0.5
Positive neutralizing anti-TCZ assay	1	0.5

Source: CSR WA19977 and 120 day safety update

In the supportive Japanese program, in study MRA319JP one patient (No. 13) became positive for neutralizing antibodies before the fourth infusion; and became positive for IgE antibodies after the fifth infusion 657 days after the fourth infusion; and was withdrawn from the study. These findings were not associated with adverse events or decreased efficacy.

In the pJIA development program, no patients experienced anaphylaxis, and no AEs were associated with anti-TCZ antibody positivity suggesting that TCZ administration in patients with pJIA is associated with low risk of clinically significant immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Relationship of AEs, SAEs and AEs of interest with respect to dosing was presented in section 7.3 Major Safety Results, Table 39 above. The dose-dependency was generally compared between the 10 mg/kg and 8 mg/kg dose groups in patients with a body weight less than 30 kg as only one dose regimen was tested for the heavier patients with a body weight of 30 kg and over. As shown in Table 39, during the open-label lead-in period (Part I), among the patients with body weight less than 30 kg, a higher proportion of patients in the 10 mg/kg group experienced AEs, infections, SAEs, and serious infections compared with the 8 mg/kg dose group, whereas no SAEs or serious infections occurred in the 8 mg. Of note, the small number of SAEs in the 10 mg/kg dose group, both of which infections characteristic for the underlying patient

population, make definitive conclusions on the dose-dependency difficult. Further, the rates in the 10 mg/kg group were comparable to the rates observed in the heavier patients treated with 8 mg/kg dose. With longer-term exposure, as of the 120-day safety update, the exposure-adjusted incidence rates for overall AEs and infections reversed and serious infections also accrued in the in the 8 mg/kg dose group.

In summary, the inconsistent trends in the overall AEs between short-term and longer-term tocilizumab exposures, and the relatively small number of SAEs and serious infections, do not indicate a clear dose-dependent increases between the 10 mg/kg and 8 mg/kg dose regimens in patients with body weight less than 30 kg. Conclusions on the dose-dependency in the heavier patients with a body weight of 30 kg and over cannot be made reliably as only one dosing regimen, 8 mg/kg, was tested in this group.

PK-Safety Relationship

To further explore the exposure-dependency of AEs, the sponsor has conducted PK-safety relationship analyses. Qualitative analyses of relative safety with regard to the dosing regimens are provided in this section.

Particular attention was paid to the open-label lead-in period where patients from all dosing regimens were exposed for the same duration, i.e. 16 weeks, allowing for head-to-head safety comparisons. As shown in Table 56, the overall safety and the most frequently reported AEs in the SOC, Infections and Infestation, and Gastrointestinal disorders, did not show a clear exposure-dependent increases by calculated PK exposure quartiles. These comparisons were further corroborated with data up to Week 40, the end of the double-blind randomized withdrawal period, where only the lowest exposure quartile had numerically smaller event rates as shown in Table 57.

Consistent with these observations, the mean exposures were also similar among patients with Grades 0, 1, 2 neutropenia and the exposure-response data on Grades 3 and 4 neutropenia are derived from single patients as shown in Table 58.

In summary, these analyses do not indicate a clear tocilizumab PK exposure dependence of clinical safety in patients with pJIA.

Table 56. Common AE Rates by System Organ Class and Preferred Term by PK Exposures Quartiles to Week 16 [AUC4wks, Cmax and Cwk16] (Part I)

Body System Preferred Terms	AUC _{4wks}			
	Q1 N=45 n [P100-PY]	Q2 N=44 n [P100-PY]	Q3 N=44 n [P100-PY]	Q4 N=44 n [P100-PY]
All Body Systems	74 [499.8]	73 [511.3]	117 [879.5]	79 [493.0]
Infections and infestation	27 [182.4]	31 [217.1]	36 [270.6]	18 [112.3]
Gastrointestinal disorders	11 [74.3]	11 [77]	20 [150.3]	17 [106.1]
	C_{max}			
	Q1	Q2	Q3	Q4
All Body Systems	78 [528.2]	81 [591.4]	93 [692.2]	91 [551.1]
Infections and Infestation	34 [230.2]	23 [167.9]	31 [230.7]	24 [145.3]
Gastrointestinal disorders	10 [67.7]	19 [138.7]	15 [111.7]	15 [90.8]
	C_{wk16}			
	Q1	Q2	Q3	Q4
All Body Systems	88 [633.5]	68 [517.0]	97 [701.3]	81 [511.3]
Infections and Infestation	33 [237.5]	21 [159.7]	30 [216.9]	21 [132.6]
Gastrointestinal disorders	10 [72.0]	10 [76.0]	19 [137.4]	19 [119.9]

Source: CSR WA19977, Table 28

Table 57. Common AE Rates by System Organ Class and Preferred Term by PK Exposures Quartiles to Week 40 (AUC4wks, Cmax and Ctough) (Parts I and II)

Body System Preferred Terms	AUC _{4wks}			
	Q1 N=19 n [P100-PY]	Q2 N=18 n [P100-PY]	Q3 N=18 n [P100-PY]	Q4 N=18 n [P100-PY]
All Body Systems	39 [468.3]	63 [885.0]	82 [1289.3]	74 [998.1]
Infections and infestation	18 [216.1]	29 [407.4]	31 [487.4]	25 [337.2]
Gastrointestinal disorders	2 [24.0]	6 [84.3]	13 [204.4]	22 [296.7]
	C_{max}			
	Q1	Q2	Q3	Q4
All Body Systems	41 [512.5]	65 [853.1]	79 [1278.5]	73 [983.5]
Infections and Infestation	20 [250.0]	28 [367.5]	26 [420.8]	29 [390.7]
Gastrointestinal disorders	3 [37.5]	9 [118.1]	12 [194.2]	19 [256.0]
	C_{tough}			
	Q1	Q2	Q3	Q4
All Body Systems	27 [352.7]	74 [1190.7]	83 [1132.0]	73 [963.6]
Infections and Infestation	18 [235.1]	27 [434.4]	28 [381.9]	29 [382.8]
Gastrointestinal disorders	-	9 [144.8]	19 [259.1]	15 [198.0]

Source: CSR WA19977, Table 34

Table 58. Summary of TCZ PK Exposures by the Worst Neutrophil CTC Grade Experienced up to Week 40 for All Patients (Parts I and II)

Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AUC _{4wks} , µg·day/mL	1285 ± 466 (1139, 656-2885) n=53	1515 ± 523 (1370, 1046-2356) n=6	1258 ± 433 (1153, 620-2002) n=12	498 -- n=1	1946 -- n=1
C _{max} , µg/mL	191 ± 42 (186, 113-312) n=53	202 ± 41 (210, 139-255) n=6	191 ± 61 (169, 118-341) n=12	118 -- n=1	272 -- n=1
C _{trough} , µg/mL	7.41 ± 8.86 (4.53, 0.0-33.2) n=53	12.41 ± 10.9 (12.24, 1.2-29.9) n=6	6.69 ± 6.47 (5.16, 0.2-20.7) n=11	0.0 -- n=1	12.62 -- n=1

Source: CSR WA19977, Table 35

7.5.2 Time Dependency for Adverse Events

The incidence of AEs is presented for both the short-term exposure, at the end of the open-label lead-in period at Week 16, and the longer-term exposure in the all exposure population as of the clinical data cut-off date in the original submission and the 120-day safety update as summarized in Table 39 and presented in section 7.3 Major Safety Results. Overall, the exposure-adjusted incidence rates of the different AEs remained stable or decreased over time suggesting that longer-exposure does not confer increased risk of cumulative toxicity.

7.5.3 Drug-Demographic Interactions

Subgroup analyses of drug-demographic interactions did not reveal consistent trends with respect to safety. However, these analyses were dependent on small numbers of patients within each group which limits the interpretation of the results and precludes definitive conclusions.

7.5.4 Drug-Disease Interactions

No specific drug-disease interactions have been noted in the pJIA development program.

7.5.5 Drug-Drug Interactions

No new data was submitted with this supplement on drug-drug interactions for review.

7.6 Additional Safety Evaluations

To further provide context to the reported safety in pJIA development program, the sponsor has summarized the experience from the adult RA and sJIA development program to allow the comparison of the relative safety across programs as shown in Table 59.

The safety database of pJIA clinical development is generally comparable to that of the sJIA program. However, it is significantly smaller than the safety database from the adult RA program which was originally used for quantitative assessment of the safety profile of tocilizumab for the original marketing approval. To account for the differences in the exposure across the different programs, the incidence of the AE is presented as exposure-adjusted event rates.

As discussed in section 7 Review of Safety above, the most common AEs and SAEs were in the SOC Infestation and Gastrointestinal Disorders. The rates of AEs in these SOC were generally twice as high in the pJIA program as in adult RA population. The rates of SAEs serious infections and AEs leading to premature withdrawal in the pJIA program were more comparable to the adult RA program.

The rates of the AEs and SAEs were highest in the sJIA program, consistent with the generally much sicker population of sJIA which is at a higher baseline risk of developing toxicities compared with the rest of the subsets of JIA or adult RA population. This is also evident by the higher mortality rates in the sJIA program.

With respect to the select laboratory abnormalities very few patients developed CTC Grade 3 or Grade 4 changes with generally comparable proportions across the three tocilizumab programs.

Table 59. Comparison of Overall Safety in pJIA Adult RA, and sJIA Development Programs

Comparison of Overall Safety in pJIA Adult RA, and sJIA Development Programs			
	pJIA	Adult RA	sJIA*
N	188	4009	112
Exposure, PY	184	14993	202
Number of patients/events (rate per 100-PY)			
All AEs	159/885 (480)	3799/45198 (301)	111/1660 (822)
<i>Infections and infestation</i>	115/302 (164)	3077/14112 (94)	102/570 (282)
<i>Gastrointestinal disorders</i>	60/131 (71)	2072/5467 (37)	67/145 (72)
Deaths	0	85 (0.6)	3 (1.5)
SAEs	17/23 (13)	1255/2194 (15)	35/47 (23)
<i>Serious infections</i>	9/9 (5)	507/668 (5)	20/22 (11)
AEs leading to withdrawal	6/6 (3)	749/754 (5)	6/6 (3)
Neutrophils decrease, n (%)			
CTC Grade 3	8 (4%)	212 (5%)	26 (23%)
CTC Grade 4	-	33 (<1%)	2 (2%)
Platelets decrease, n (%)			
CTC Grade 3	1 (<1%)	18 (<1%)	1 (1%)
CTC Grade 4	1 (<1%)	14 (<1%)	-
ST elevation, n (%)			
CTC Grade 3	3 (2%)	35 (<1%)	3 (3%)
CTC Grade 4	-	3 (<1%)	1 (1%)
ALT elevation, n (%)			
CTC Grade 3	3 (2%)	129 (3%)	9 (8%)
CTC Grade 4	-	6 (<1%)	1 (1%)
Total bilirubin elevation, n (%)			
CTC Grade 3	1 (<1%)	2 (<1%)	-
CTC Grade 4	-	1 (<1%)	-

Source: Summary of Clinical Safety, Adapted from Tables 24, and 25 and 120-day safety update
 *the clinical data cut-off for the sJIA program is as of May 31, 2011, the two-year data from the ongoing study WA18221

In summary, the safety profile of pJIA program is as expected for the study population and consistent with the overall safety profile of tocilizumab in adult RA patients. While reassuring that no malignancies or anaphylaxis were reported in the pJIA program, the safety database is relatively small and with relatively short duration of exposure to mitigate the concerns with the potential risk of such toxicities. Both events are labeled and a part of the REMS.

7.6.1 Human Carcinogenicity

No malignancies were reported in the pJIA development program.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in the pJIA development program.

7.6.3 Pediatrics and Assessment of Effects on Growth

The pJIA program was not designed to specifically address the effects of TCZ on growth and no specific information on pediatrics and assessment on growth were provided with this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No TCZ overdose cases have been reported for pJIA studies. No new information is provided in this submission on drug abuse potential, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Tocilizumab has a marketing license in Japan and has been available for treatment of multicentric Castleman's disease in Japan since 2005 through a closed distribution program, and for treatment of RA, pJIA and sJIA since April 2008. Therefore, the postmarketing data submitted in this efficacy supplement are derived from the following sources:

- Japanese postmarketing study ML21939 for pJIA and adult RA
- Japanese postmarketing study ML21940 for sJIA
- Spontaneous reports received globally, including those from non-interventional studies for patient treated for pJIA, sJIA, JIA that are unspecified by classification, and in pediatric patients under the age of 18 years treated with tocilizumab for unknown indications. Importantly 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 reported as of July 31, 2012.

8.1 Japanese postmarketing surveillance (JPMS) study ML21939 for pJIA

A total of 179 patients with pJIA have been enrolled with 94 patient-years of exposure. These patients were evaluated for baseline characteristic, adverse drug reactions, events of interest (infection, gastrointestinal perforation, cardiac dysfunction, malignant tumor, anaphylactic shock, anaphylactoid symptoms, infusion reactions, lipid-related test abnormalities), and deaths for 6 months after the start of tocilizumab treatment (the

observation period). The following is a summary of the reported safety in study ML21939:

- There were no deaths reported in this study.
- Approximately 40% (70/179) of patients reported adverse drug reaction (ADR) with an overall incidence of 147 events per 100 PY consistent with the rates in study WA19977.
- The incidence of serious ADRs was 7% (13/179) with incidence of 19 events per 100 PY, which is higher than in study WA19977.
- Infections were the most common ADR with incidence of about 52 events per 100 PY.
- Serious infections occurred at 9 events per 100 PY (enteritis infectious, cellulitis, mumps, pneumonia mycoplasmal, pyelonephritis and septic shock), an incidence and types of infections comparable to the study WA19977.
- One patient developed a perforated gastric ulcer; the case is confounded by concomitant ibuprofen use.
- No events of malignancy were reported
- No events of anaphylaxis were reported
- No events of demyelinating disorder were reported
- Laboratory abnormalities were observed at rates and severity similar to study WA19977.

In summary, the systematically reported postmarketing experience in study ML21939 is consistent with the overall safety profile of tocilizumab identified in study WA19977.

8.2 Postmarketing spontaneous reports in pJIA

Table 60 summarizes the SAEs from the Japanese postmarketing study ML21940 for sJIA and the spontaneous reports received globally, including those from non-interventional studies for patient treated for pJIA, sJIA, JIA that are unspecified by classification, and in pediatric patients under the age of 18 years treated with tocilizumab for unknown indications, reported as of July 31, 2012. The interpretation of these data is complicated by the uncertainty surrounding the denominator with respect to the number of patients treated and the duration of exposure. Therefore, the comparisons are generally qualitative.

A total of 26 SAEs were reported in patients with the diagnosis of pJIA (Table 60, Column A). The distribution of the events is consistent with the previously established safety profile in this population.

- One death was reported:
 - AER 1086648: A 37-year-old male patient with a history of pJIA Adult Onset Still's Disease who was reported as being treated with TCZ for hemophagocytic syndrome. A bladder biopsy revealed that the patient had lymphoma of the bladder. The patient had developed a high fever, which was unresponsive to steroid treatment. He then developed cytokine storm

and multiple organ failure for which he was given one dose of TCZ in an attempt to treat the hemophagocytic syndrome, but the patient died. While this event was reported under pJIA, the diagnosis of adult onset Still's disease is generally regarded as the adult equivalent of sJIA. Therefore, the case should have been reported under the diagnosis of sJIA.

- Infections were the leading cause of SAEs with 4 cases of pneumonia, one-bronchitis, one-gastroenteritis.
- One case of interstitial lung disease was reported in a 9-year-old female patient who was on concomitant methotrexate; the case was treated successfully with systemic corticosteroids and the patient tolerated re-challenge with tocilizumab without complications.
- One case of ventricular arrhythmia and cerebral infarction within two weeks of initiating tocilizumab was reported in a 37-year-old female patient; the event was attributed to the long-standing (34 years) of the underlying disease.
- One 17-year-old female patient developed anaphylactic reaction (reported as seven different events) in the middle of her third infusion which was successfully treated with methylprednisolone and permanent discontinuation of tocilizumab.

Table 60. Summary of SAEs from Postmarketing Reports for pJIA, sJIA, Unspecified JIA and Unknown Indications

Summary of SAEs from Postmarketing Reports for pJIA, sJIA, Unspecified JIA and Unknown Indication						
	Column A: Spontaneous pJIA	Column B: sJIA study ML21940	Column C: Spontaneous sJIA	Column D: Unspecified JIA	Column E: Unknown indication	Total
No of SAEs	26	254	125	144	26	577
No of patients	13	123	64	74	12	285
Age range, years	3-37	0.3-34	1-46	2-70	11-55	0.3-70
SAE by SOC, n (%)						
Infections	6 (23%)	81 (32%)	39 (31%)	21 (15%)	1 (4%)	149 (26%)
Gastrointestinal	1 (4%)	24 (9%)	7 (6%)	12 (8%)	3 (12%)	48 (8%)
Musculoskeletal	0	15 (6%)	5 (4%)	16 (11%)	2 (8%)	38 (7%)
General	7 (27%)	8 (3%)	13 (10%)	13 (9%)	3 (12%)	46 (8%)
Investigations	1 (4%)	24 (11%)	8 (6%)	5 (4%)	1 (4%)	44 (8%)
Neoplasms	0	28 (11%)	6 (5%)	3 (2%)	1 (4%)	38 (7%)
Blood disorders	0	14 (6%)	4 (5%)	7 (5%)	1 (4%)	26 (5%)
Respiratory	3 (12%)	13 (5%)	8 (6%)	7 (5%)	3 (12%)	34 (6%)
Nervous system	1 (4%)	9 (4%)	4 (5%)	4 (3%)	1 (4%)	19 (3%)
Skin disorder	1 (4%)	6 (2%)	5 (4%)	15 (10%)	2 (8%)	34 (6%)
Vascular disorder	0	5 (2%)	2 (2%)	7 (5%)	3 (12%)	19 (3%)
Immune disorder	1 (4%)	2 (<1%)	6 (5%)	9 (6%)	0	18 (3%)
Injury Poisoning	0	9 (4%)	5 (4%)	5 (4%)	0	19 (3%)
Hepatobiliary	1 (4%)	9 (4%)	0	2 (1%)	0	12 (2%)
Renal	0	5 (2%)	2 (2%)	0	3 (12%)	10 (2%)
Cardiac	1 (4%)	1 (<1%)	6 (5%)	5 (4%)	0	13 (2%)
Pregnancy	0	1 (<1%)	0	0	0	1 (<1%)
Reproductive	0	0	0	0	1 (4%)	1 (<1%)
Ear	0	0	1 (<1%)	1 (<1%)	0	2 (<1%)
Psychiatric	0	0	1 (1%)	0	0	1 (<1%)
Eye	0	0	0	1 (<1%)	1 (10%)	2 (<1%)
Surgical	0	0	1 (<1%)	0	0	1 (<1%)

Source: 120-day safety update, adapted from tables 20, 21, 23, and 24, Data as of July 31, 2012

8.3 Japanese postmarketing surveillance (JPMS) study ML21940 for sJIA and spontaneous reports for other pediatric populations exposed to tocilizumab

Japanese postmarketing surveillance study ML21940

A total of 123 patients with sJIA were enrolled in the JPMS with a total of 254 SAEs as of the clinical data cut-off for the study July 31, 2012 (Table 60, Column B). Below is the summary of the safety findings:

- There were five deaths reported in the Japanese PMS study ML21940

- MCN 588086: A 1-year 8-month-old patient who died of acute respiratory distress syndrome. She also had concurrent pneumonia, interstitial lung disease, protein-losing gastroenteropathy, decreased blood pressure, hypertension, allergic dermatitis, bronchitis, flushing, acute renal failure, vomiting, anemia, gastroenteritis, and hypercoagulation. Her medical history included congenital anomaly, hepatomegaly, anemia, lung disorder, lymphadenopathy, pericarditis, renal aplasia, renal hypertension, renal impairment, renal tubular disorder, serositis, rash, and small size at birth.
- MCN 624762: A four-month old patient who died of pseudomonas infection, sepsis, and interstitial lung disease. He also had concurrent respiratory syncytial virus infection, pancytopenia, skin necrosis, and renal impairment. His medical history included decreased white blood cell count, platelet transfusion, anemia, disseminated intravascular coagulation hepatomegaly, histiocytosis haematophagic, and skin necrosis
- MCN 725800: A 2-year old male patient who died of cardiac failure, vasculitis, respiratory failure, renal failure, and hepatic failure.
- AER 1057932: A 9-year old female patient experienced SAEs of catheter infection, MAS, gastric ulcer haemorrhage, sepsis, pneumothorax, fatal haemorrhage, fatal haemorrhagic shock, and fatal pneumocystis pneumonia. After approximately 22 months of TCZ treatment, the patient developed pneumocystic jiroveci pneumonia. Two weeks later, she developed MAS; despite treatment with steroids and cyclosporine, her condition worsened and died due to the events.
- AER 1058658: A 7-year old male patient experienced a SAE of MAS and fatal pulmonary haemorrhage. The patient had a history of MAS and disseminated intravascular coagulation (DIC), hepatic failure, and transfusion prior to starting TCZ. Approximately 1 year after beginning TCZ treatment, the patient developed mumps, hepatic function disorder and DIC. He later developed MAS, DIC and hepatic function abnormal, which were at first stabilized with steroid pulse therapy and plasma diafiltration treatment; however, the events recurred.
- The most common SAEs were serious infections across all categories, consistent with the experience in the pJIA, sJIA and adult RA programs.
- 81 serious infections were reported with pneumonia being the most common (n=15) followed by gastroenteritis (n=11) and bronchitis (n=7); three of the infections were fatal as described above, including a case of the opportunistic infection Pneumocystic jiroveci pneumonia.
- Investigations SAEs were mostly associated with know hematologic abnormalities.
- All 28 cases reported under neoplasm SOC in the Japanese postmarketing study ML21940 for sJIA were cases of macrophage activation syndrome (MAS), expected in the sJIA population and consistent with the clinical trial experience.

- There were two events of gastrointestinal perforations in this study confounded by co-morbidities and concomitant medications.
- There were 2 events of hepatic function abnormalities. One event resolved after temporary discontinuation of TCZ treatment; no other clinical details were provided. The other event occurred in the setting of critical illness (AER 1058658 above).

Postmarketing spontaneous reports in the rest of the pediatric populations (sJIA, unspecified JIA, unknown indications) exposed to tocilizumab

Among the rest of the spontaneous reports, a total of 295 SAEs were reported in 150 patients with the bulk of the data coming from the sJIA or unspecified JIA indications (Table 60, Columns C, D, and E).

- There were eight deaths reported in this group.
 - MCN 1018761: A 29-year-old female patient suffered a fatal myocardial infarction three months after initiating tocilizumab; the event was confounded by co-morbidities of diabetes mellitus, hypertension, and renal insufficiency, and a prior history of MI
 - MCN 745048: A 56-year old female patient in Canada experienced a fatal event of juvenile arthritis. No details regarding the patient's death were reported.
 - AER1079059: A female sJIA patient of unknown age from Thailand developed an infection and was hospitalized after an unknown duration of treatment with TCZ. It was suspected that the patient was neutropenic at the time she became septic. It was also suspected that the patient was experiencing concurrent hemophagocytosis.
 - AER 1024688: A female patient from Russia, age unknown, developed an unspecified generalized infection. No details were reported.
 - AER 1051453: A 45-year old female patient developed fatal pancreatitis and fatal myocardial infarction after approximately 1 year of treatment with TCZ. The patient had been experiencing recurrent pancreatitis, and had biliary surgery one month prior to the cardiac arrest. Limited information was provided for this case.
 - AER1069916: A 36-year old female patient from Canada treated for an unspecified form of JIA was reported to have died approximately 5 months after beginning treatment with TCZ. The reporter declined to provide additional details.
 - AER 1082503: A literature report of 89 patients treated with TCZ described one event of fatal sepsis. No specific patient details were provided, but it was not specified if the patients had sJIA or had been treated for another indication.
 - AER 1083032: A literature report of 81 patients treated for RA and unspecified JIA conditions reported "death" in one unidentified patient. It was not specified in the patient was treated for RA or JIA.

- Serious infections were the most common SAE with pneumonia being the most common serious infection.
- Notably, there were several reports of hypersensitivity reactions, including 7 events of anaphylactic reaction, 2 event of anaphylactic shock and several events reported as infusion-related reactions, none of which fatal. Most of the events occurred within the first 2 to 4 tocilizumab infusions with the exception of two events of anaphylaxis which occurred on the 6th and 8th infusion each. This experience is consistent with the experience reported in adult RA and is a labeled event.
- Two events of gastrointestinal perforation occurred in adults with a diagnosis of sJIA (28-year-old male) and unspecified JIA (60-year-old female). Both cases were confounded by concomitant medications to include systemic corticosteroids and NSAIDs and in one of the cases by co-morbidity of appendicitis.
- Ten cases of MAS were reported in this group.
- No malignancies were reported.
- Two events in SOC Hepatobiliary disorders were reported. One was a case reported as a drug-induced liver injury in a 7-year-old male patient with JIA (AER1063028) who was also taking concomitant methotrexate and leflunomide which was treated with discontinuation of all three drugs and did not recur upon re-challenge with tocilizumab The second case was diagnosed with EBV viral hepatitis. No cases met the Hy's law criteria.

In summary, the post-marketing experience reviewed in this section indicates a safety profile of tocilizumab with respect to the types, severity and distribution of SAEs was consistent with the clinical trials experience and the underlying patient population of patients with JIA.

9 Appendices

9.1 Literature Review/References

Sampson HA, et al. Second symposium on the definition of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. JACI 2006;117(2):391-7

9.2 Labeling Recommendations

Labeling Pertaining to Efficacy

I recommend the following major efficacy-related revisions:

1. Removal of the proposed Table (b) (4) for the following reasons:
 - a. Even though the table represents the (b) (4) the table does not provide essential information beyond the (b) (4)
 - b. The data in the table, as presented, may not be easily interpretable and may be confusing to prescribers as it implies (b) (4)
 - c. The table does not account for the fact tha (b) (4)
 - d. Lastly, this is a departure from the format of labeling the similar data in already approved products for the same indication.
2. Addition of information on the additional treatment benefit of MTX for the following reasons:
 - a. Currently tocilizumab is labeled as “ACTEMRA may be used alone or in combination with methotrexate” without providing further guidance to prescribers.
 - b. The subpopulation analyses from study WA19977 based on MTX use at baseline as a stratification variable, indicated that use of background MTX provided additional clinical benefit independent of that of tocilizumab as discussed in section 6.1.7 Subpopulations and Table 29, Table 30, and Table 31. These data provide additional guidance to prescribers that some pJIA patients treated with tocilizumab monotherapy may benefit from

addition of MTX. While intuitive, this is clinically useful information which warrants being included in labeling.

Suggested language (in **bold, red**) for inclusion of the additive benefit of MTX in labeling in section 14, second paragraph in the subheading “Polyarticular Juvenile Idiopathic Arthritis”:

*“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** (b) (4) **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 (b) (4) %, and (b) (4) %, respectively.*

3. Provide accompanying text to Table 4, “Proportions of Patients with DAS28-ESR Less Than 2.6 with Number of Residual Active Joints”. While unrelated to this application, such text will provide context for the interpretation of the efficacy findings.

Labeling Pertaining to Efficacy

I recommend that the text “all exposure population” is defined to provide context for the safety data interpretation. The all exposure analysis population was defined as all patients who received at least one dose of study drug and had at least one post-randomization assessment of safety.

9.3 Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee (AAC) was convened on July 29, 2008 to discuss the clinical data in the original tocilizumab BLA submission. The members of the committee concurred that efficacy was demonstrated in RA. They were uncertain whether the data clearly indicated a benefit of 8 mg/kg over the 4 mg/kg dose in patients with an inadequate response to DMARDs, as some members noted that the components of the ACR response criteria showed little difference between doses with the exception of effect on C-reactive protein (CRP) levels. The risk of serious infection was considered to be similar to that seen with commonly used agents in RA. GI perforation and demyelination adverse events were considered in light of their relative rarity, and the risks of these were not felt to outweigh the potential benefits observed with the product. The main area under discussion was the potential risk conferred by the

elevation in LDL levels. Some members expressed great concern while other members were reassured by the lack of a signal for clinical cardiovascular events and by the potentially beneficial anti-inflammatory effects of tocilizumab on cardiovascular risk. The committee voted 10-to-1 in favor of approval.

No new Advisory Committee (AC) meeting was deemed necessary for this submission as no issues were identified during the review process to warrant AC discussion.

9.4 Individual Study Reports

9.4.1 Study WA19977

9.4.1.1 Study WA19977: Design

This is an ongoing three-part Phase 3 study to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in patients with active pJIA. The study design is summarized in Figure 2. The targeted population consisted of patients who had shown an inadequate response to MTX or were intolerant to MTX. However, concomitant MTX was permitted during the study.

- Part I (complete) was a 16-week open-label TCZ treatment lead-in period:
 - All patients weighing at least 30 kg received 8 mg/kg TCZ IV every 4 weeks (q4w).
 - Patients weighing less than 30 kg were randomized in a 1:1 ratio to either 8 mg/kg or 10 mg/kg TCZ q4w.
 - Efficacy was assessed using the JIA American College of Rheumatology (ACR) response measure. Patients who achieved at least a 30% improvement (i.e., a JIA ACR30 response) at week 16 compared to baseline were eligible to enter Part II.
- Part II (complete) was a 24-week randomized, double-blind, placebo-controlled withdrawal period in which patients were randomized in a 1:1 ratio to treatment with TCZ at the same dose level as in Part I or to placebo. Randomization was stratified by concomitant MTX use and concomitant oral corticosteroid use. Patients who developed a JIA ACR30 flare relative to week 16 qualified for escape therapy with TCZ at the same dose as in Part I.
- Part III (ongoing) is a 64-week open-label period beginning at week 40 (or once a patient entered escape therapy with TCZ) to examine the long-term use of TCZ on safety and efficacy. In patients originally randomized to the TCZ 10 mg/kg dose, the investigator had the option to reduce the TCZ dose level to 8 mg/kg if the patient's body weight had increased to ≥ 30 kg and was

at least 5 kg above the baseline weight for three consecutive visits. Part III is ongoing. The last patient's last visit is expected for September 2012.

Escape criteria

The IVRS decision when considering a site request for escape due to inadequate response will be based on JIA ACR30 flare definition relative to week 16 (delineated in Appendix 2 of the protocol and reproduced below. The JIA ACR Core Set Variables recorded by the site will undergo quality checks by the Collaborative Groups and a JIA ACR response calculated utilizing all six of the JIA ACR Core Set Variables.

If JIA ACR30 flare criteria are met (and confirmed by the collaborative groups) at a regularly scheduled infusion visit in Part II of the study the subject may enter escape and receive standard of care such as intra-articular injections or an increase in prednisone up to a maximum of 10 mg/day or 0.2mg/kg (whichever is less) equivalent in addition to receiving open-label TCZ at that visit.

If a flare is suspected at a non-infusion but scheduled visit in Part II then additional flare assessments must be completed as outlined in the Schedule of Assessments. If flare is suspected outside the windows of a scheduled visit (either infusion or non-infusion) assessments including all flare assessments should be completed using the unscheduled visit template in the eCRF. If escape criteria are met (based on collaborative group approval) then after all assessments have been completed the subject may enter escape and receive standard of care such as intraarticular injections or an increase in prednisone up to a maximum of 10 mg/day or 0.2mg/kg (whichever is less) equivalent. Open-label TCZ can be administered at the next scheduled infusion visit.

Inclusion Criteria:

1. Diagnosis of pJIA (RF positive or negative JIA polyarthritis subset (pJIA) for at least 3 months) or extended oligoarticular JIA (eoJIA) with active polyarticular course for at least 3 months prior to study entry according to ILAR Criteria⁸. Subjects with pJIA: requiring presence of active disease with at least five joints with active arthritis (joints that are swollen or if no swelling is present limitation of movement accompanied by pain, tenderness or both) at screening and baseline (with at least three of the active joints having limitation of motion).
2. Age 2 to 17.
3. Must meet one of the following
 - a. Inadequate response to MTX or
 - b. Inability to tolerate MTX.
4. Must meet one of the following:
 - a. Not receiving MTX, or discontinued MTX at least 4 weeks prior to baseline visit or
 - b. Taking MTX for at least 12 weeks immediately prior to the baseline visit and on a stable dose of ≥ 10 to ≤ 20 mg/m² for at least 6 weeks prior to

the baseline visit, together with either folic or folinic acid according to local standard of care.

5. Must meet one of the following
 - a. Not currently receiving oral corticosteroids, or
 - b. Taking oral corticosteroids at a stable dose for a minimum of 4 weeks prior to the baseline visit at no more than 10 mg/day or 0.2 mg/kg/day, whichever is less.
6. Fertility
 - a. Female not of child-bearing potential or
 - b. Female of child-bearing potential practicing effective contraceptive measures, having a negative pregnancy test within three weeks prior to randomization; or
 - c. Sterile male or
 - d. Non-sterile male practicing effective contraceptive measures with female partner of child-bearing potential.

[Females of childbearing potential must be using a reliable means of contraception (abstinence being a possible option) throughout the study and up to 12 weeks after the last infusion of study drug]
7. Must meet one of the following:
 - a. Not taking NSAIDs or
 - b. Taking no more than 1 type of NSAID at a stable dose for a minimum of 2 weeks prior to the baseline visit and is less than or equal to the maximum recommended daily dose.
8. Must meet one of the following
 - a. Never treated with biologics or
 - b. If previously treated must have discontinued etanercept \geq 2 weeks prior to baseline, infliximab or adalimumab \geq 8 weeks prior to baseline, anakinra $>$ 1 week prior to baseline or abatacept \geq 12 weeks prior to baseline.
9. Written informed consent for study participation obtained from parents or legal guardian, with assent as appropriate by the subject, depending on the level of the subject's understanding.

Exclusion Criteria:

General

1. Wheelchair bound or bedridden or has little or no ability for self-care.
2. Any other autoimmune, rheumatic disease or overlap syndrome other than the permitted pcJIA (Rf pos or neg) and extended oligoarticular JIA. The excluded illnesses include but are not limited to systemic JIA, Lyme disease, enthesitis-related arthritis, psoriatic arthritis, Reiter's syndrome, SLE, infectious or reactive arthritis or parvovirus infections.
3. Not fully recovered from recent surgery or less than six weeks since surgery, at the time of screening visit; or planned surgery during the initial 40 weeks of the study.

4. Lack of peripheral venous access or unwilling to undergo multiple venipunctures.

General Safety

1. Pregnant, lactating or intending to become pregnant during study conduct and up to 12 weeks after the last administration of study drug
2. Any significant concurrent medical or surgical condition which would jeopardize the subject's safety or ability to complete the trial.
3. History of significant allergic or infusion reactions to prior biologic therapy.
4. History of or currently active primary or secondary immunodeficiency.
5. History of alcohol, drug or chemical abuse within 1 year of screening.
6. Evidence of serious uncontrolled concomitant diseases including but not limited to the cardiovascular, pulmonary, nervous, renal, hepatic or endocrine system.
7. Any active acute, subacute, chronic or recurrent bacterial, mycobacterial, viral or systemic fungal infection or opportunistic infection.
8. Active TB requiring treatment within 2 years prior to screening visit or currently active TB
9. Positive PPD at screen unless chest radiograph is negative for active tuberculosis at screen and subject treated with anti-tuberculosis therapy prior to receiving study medication.
10. Any major episode of infection requiring hospitalization or treatment during screening or treatment with IV antibiotics completed within 4 weeks of screening visit or oral antibiotics completed within 2 weeks of the screening visit.
11. Known active current or history of recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infections (e.g. bronchiectasis), an open or draining or infected skin wound, sinusitis, recurrent urinary tract infection (e.g. recurrent pyelonephritis).
12. History of reactivation or new onset of a systemic infection such as herpes zoster or Epstein Barr virus within 2 months of the screening visit.
13. Hepatitis B sAg or hepatitis C Ab positive.
14. Chronic hepatitis.
15. Significant cardiac [e.g. congenital heart disease, valvular heart disease, valvular heart disease, constrictive pericarditis, myocarditis] or pulmonary disease (e.g. asthma and cystic fibrosis).
16. Asthma for which the subject has required the use of oral or parenteral corticosteroids for ≥ 2 weeks within 6 months prior to the baseline visit.
17. History or concurrent serious gastrointestinal disorders such as ulcer or inflammatory bowel disease, Crohn's disease, ulcerative colitis or other symptomatic lower gastrointestinal conditions, including ulcer and perforation. History of or known or current malignancy or lymphoma or findings suggestive of lymphoma such as clinically significant splenomegaly or unusual lymphadenopathy.
18. Uncontrolled diabetes mellitus defined as Hgb A1c $\geq 8.8\%$ for children < 12 and Hgb A1C $> 10\%$ for children ≥ 12 years old.
19. History of acute or chronic uveitis.

20. Prior history of infected joint prosthesis, or having received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

Excluded Previous or Concomitant Therapy

1. Participation in another interventional clinical trial within the past thirty days or five serum half-lives or the pharmacodynamic effect of the investigative medication, whichever is longer.
2. Previous treatment with TCZ.
3. Intra-articular, intramuscular, intravenous or long-acting (such as dexamethasone) corticosteroids including ACTH during the 4 weeks prior to the baseline visit.
4. Treatment with DMARDs (other than MTX) or immunosuppressants, including but not limited to: HCQ, chloroquine, gold, azathioprine, D-penicillamine, sulfasalazine, cyclosporine or thalidomide within 4 weeks prior to the baseline visit.
5. Treatment with leflunomide within 4 weeks prior to the first administration of study drug (irrespective of undergoing a drug elimination procedure) or have received leflunomide within 3 months prior to the first administration of study agent and have not undergone a drug elimination procedure which was not followed by standardized cholestyramine washout and documented leflunomide level to be below the limit of detection prior to the baseline visit.
6. Treatment with cyclophosphamide within 12 months prior to the baseline visit.
7. Treatment with etoposide (VP16) within 3 months prior to the baseline visit.
8. Administration of intravenous immunoglobulin for the treatment of active polyarticular disease within 4 weeks prior to the baseline visit.
9. Previous treatment with any cell depleting therapies, including investigational agents (e.g. anti-CD19 and anti-CD20).
10. Prior stem cell transplant at any time.
11. Live or attenuated vaccines within 4 weeks prior to the baseline visit, or intending to receive while on study medication or 12 weeks following the last dose of study medication.

Laboratory Exclusions

1. Serum creatinine >1.5x ULN for age and sex.
2. AST or ALT >1.5x ULN for age and sex.
3. Total bilirubin >1.3 mg/dL
4. Platelet count <150 x 10³ /uL

Concomitant Medication and Other Treatments:

DMARDs

- MTX is permitted but not required. If MTX is discontinued, it needs to have been done so at least 4 weeks prior to baseline visit. Patients on MTX should have been taking it for at least 12 weeks prior to baseline visit, with stable dose <20

mg/m² for at least 8 weeks, along with supplemental folic acid or folinic acid. MTX may be reduced at any time for safety reasons, and may be reduced for efficacy in Part II for those patients in clinical remission for 6 months and off all corticosteroids.

- Leflunomide is not allowed, and levels must be below the limit of detection prior to baseline.
- Cyclophosphamide is not allowed during the study and for 3 months prior to baseline visit.
- Etoposide (VP16) is not allowed during the study and for 3 months prior to baseline visit.
- Other DMARDs (except MTX) are not allowed and must have been discontinued 6 weeks prior to baseline, including but not limited to: hydroxychloroquine, chloroquine, gold, azathioprine, D-penicillamine, sulfasalazine, cyclosporine, and thalidomide.

Biologics*

- Etanercept is not permitted and must have been discontinued >2 weeks prior to baseline.
- Anakinra is not permitted and must have been discontinued >1 week prior to baseline.
- Abatacept is not permitted and must have been discontinued >12 weeks prior to baseline.
- Infliximab and adalimumab are not permitted and must have been discontinued >8 weeks prior to baseline.
- Patients previously treated with tocilizumab are not permitted in the study. * Enrollment will be limited to not exceed 55 subjects (30% of 185 pc subset) with prior exposure to a biologic.

Steroids

- Subjects may be taking oral corticosteroids at a stable dose for a minimum of 4 weeks prior to the baseline visit at no more than 10 mg/day or 0.2 mg/kg/day, whichever is less.
- Intra-articular, intramuscular, intravenous or long-acting (such as dexamethasone) corticosteroids including ACTH are not permitted within 4 weeks prior to the baseline visit.
- Intramuscular and intravenous steroids are not allowed at any time during the study for treatment of pJIA.
- Injection of intra-articular corticosteroids during the active treatment TCZ lead-in period is not permitted in Part I. It is also not permitted to administer intra-articular injections, tendon sheath or bursa injections during the double-blind withdrawal period (Part II; week 16 to 40 inclusive) unless and until the subject has already qualified for escape with a JIA ACR30 flare relative to week 16 and all assessments for that visit have been completed; or the patient has completed Part II (week 40). Injections may be given subsequent to but not prior to the

subject entering escape as these injections could affect the primary endpoint for the study or escape criteria.

- During open-label treatment phase III (at or after week 40), subjects undergoing an intraarticular, tendon sheath or bursa injection will continue to receive study drug infusions and evaluations as long as a significant clinical response (JIA ACR30) to TCZ relative to baseline is maintained.
- Concomitant medications may be reduced for efficacy only according to protocol in the respective order (oral corticosteroids first, methotrexate second and NSAIDs last) in Part III of the study.
- Corticosteroids can be increased for reasons of safety (e.g. asthma attack) to a maximum of 30 mg/day or 0.5 mg/kg/day prednisone or equivalent whichever is less for a maximum dosing period of <14 days after which the corticosteroid dosage must be returned to baseline. This is permitted only once in a 6 month period.

NSAIDs

- NSAIDs are permitted, only 1 type, and at stable dose (no greater than maximum recommended dose) for >2 weeks prior to baseline.
- Dose must remain stable during Parts I and II of the study.
- After Part II, may be lowered for reasons of safety; but for efficacy may only be tapered after steroids and MTX have been discontinued and patient has been in clinical remission for >6 months (Appendix 9).

Immunoglobulin

- Not permitted during the study or within 4 weeks prior to baseline visit. Varicella-Zoster Immunoglobulin
- Permitted for treatment of Herpes Zoster/Varicella adverse events or exposure

Acetaminophen/paracetamol

- Normal, but not extended, release may be used as needed, but should not be taken within 6 hours prior to a study visit where clinical efficacy assessment will be performed.

Iron

- May be given to patients anemic at screening if anemia is likely due to anemia of chronic disease or iron deficiency and there is no contraindication to use.

Folic or folinic Acid

- All patients on MTX must receive at least the minimum recommended dose as per local standard of care.

Topical anesthetics

- May be used prior to IV or venipuncture procedures base on local guidelines

Other prohibited concomitant medications

- Live or attenuated vaccines within 4 weeks of baseline, during the study, or 12 weeks following the last administration of study medication
- Cell-depleting therapies (e.g. anti-CD19 or anti-CD20) at any time previous or during the study
- Stem cell transplant at any time previous

Dosage and Administration

- Part I: Active treatment lead-in period, every 4 weeks for 4 doses.
 - < 30 kg randomized 1:1 to either 8 mg/kg or 10 mg/kg
 - ≥ 30 kg 8 mg/kg
- Part II: Double-blind withdrawal period. All subjects were randomized to either
 - TCZ (at the same dose as Part I)
 - Placebo
- Part III: Open-Label (Part I dose resumed)

Safety Monitoring

Table 61. Schedule of Assessments in Study WA19977

Visit	Active treatment Period - Part I									Double-Blind Withdrawal - Part II								
	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study Day	-21	0	7±3	14±3	28±3	42±3	56±3	70±3	84±3	112±3	126±3	140±3	154±3	168±3	196±7	224±7	252±7	280±7
Weeks from baseline	-3	0	1	2	4	6	8	10	12	16 ⁵	18 ²¹	20	22 ²¹	24	28	32	36	40
Informed Consent ¹	X																	
Inclusion / Exclusion	X	X																
Demographics	X																	
Medical History ²	X	X																
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB test ³	X																	
CXR ⁴	X																	
ECG ¹⁷	X																	
Clinical Assessments																		
Height/Weight	X	X		X	X		X		X	X		X		X	X	X	X	X
Vital Signs	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X								X								
Blinded Joint Count	X	X		X	X		X		X	X	F ²¹	X	F ²¹	X	X	X	X	X
Parent Global		X		X	X		X		X	X	F ²¹	X	F ²¹	X	X	X	X	X
MD Global		X		X	X		X		X	X	F ²¹	X	F ²¹	X	X	X	X	X
CHAQ		X		X	X		X		X	X	F ²¹	X	F ²¹	X	X	X	X	X
Tanner Score	X																	
JADI ⁷		X																
Inactive Disease ⁸				X	X		X		X	X	F ²¹	X	F ²¹	X	X	X	X	X
Wrist Hand X-rays ⁹		X																

Visit	Active Treatment Period - Part I									Double-Blind Withdrawal - Part II								
	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study Day	-21	0	7±3	14±3	28±3	42±3	56±3	70±3	84±3	112±3	126±3	140±3	154±3	168±3	196±7	224±7	252±7	280±7
Weeks from baseline	-3	0	1	2	4	6	8	10	12	16 ⁵	18 ²¹	20 ²¹	22 ²¹	24 ²¹	28 ²¹	32 ²¹	36 ²¹	40
Fasting Laboratory Tests ¹⁰		X					X			X								
Screening Laboratory Tests	X																	
Hematology	X	X	X	X	X		X		X	X		X		X	X	X	X	X
Reticulocytes		X	X	X	X		X		X									
Pregnancy (Urine) ¹¹		X		X	X		X		X	X		X		X	X	X	X	X
Chemistry Panels 1 and 2 ²⁰	X	X			X		X		X	X		X		X	X	X	X	X
Lipid Profile Panel 1		X					X			X	F ²¹	F ²¹	F ²¹	F ²¹	F ²¹	F ²¹	F ²¹	F ²¹
Lipid Profile Panel 2		X																
ESR ¹²		X		X	X		X		X	X	X	X	X	X	X	X	X	X
CRP ¹³		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology Profile		X																
Pharmacokinetic/Pharmacodynamic, IL-6, sIL-6R, TCZ ^{15,16}		X ^{15,16a}	X ^{16b}	X ^{16b}	X ^{15,16a}	X ^{16b}	X ^{15,16a}	X ^{16b}	X ^{15,16a}	X ¹⁵	X ^{16b}	X ¹⁵	X ^{16b}	X ¹⁵	X ¹⁵	X ¹⁵	X ¹⁵	X ¹⁵
Anti-TCZ Antibody		X ¹⁵									F ²¹	F ²¹	F ²¹	F ²¹	F ²¹	F ²¹	F ²¹	X ¹⁵
Sex Hormones		X																
Dipstick Urinalysis ¹⁴		X								X								
Infusions ⁵		X			X		X		X	X		X		X	X	X	X	X

Primary Clinical Review
 Reviewer: Nikolay P. Nikolov, M.D.
 BLA 125,276, supplement 64
 tocilizumab (Actemra)

Visit	Open Label Part III															33 ¹⁹	34 ¹⁹	35 ¹⁹
	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	W/D 1	W/D 2	W/D 3
Study Day	308 ±7	336 ±7	364 ±7	392 ±7	420 ±7	448 ±7	476 ±7	504 ±7	532 ±7	560 ±7	588 ±7	616 ±7	644 ±7	672 ±7	700 ±7	728 ±7	756	784
Weeks from baseline	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	+4	+4
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TB test ³			X												X			
CXR ⁴			X															
Height/Weight ⁵	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination			X							X						X	X ¹⁸	X ¹⁸
Unblinded Joint Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Parent Global	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MD Global	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CHAQ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Tanner Score			X							X						X		
JADI ⁷			X							X						X		
Inactive Disease/Remission ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Wrist Hand X-rays ⁹			X													X		

Visit	Open Label Part III															33 ¹⁹	34 ¹⁹	35 ¹⁹
	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	W/D 1	W/D 2	W/D 3
Study Day	308± 7	336± 7	364± 7	392 ±7	420 ±7	448 ±7	476 ±7	504 ±7	532 ±7	560 ±7	588 ±7	616 ±7	644 ±7	672 ±7	700 ±7	728 ±7	756	784
Weeks from baseline	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	+4	+4
Fasting Laboratory Tests ¹⁰			X							X						X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy (Urine) ¹¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel 2		X		X		X		X		X		X		X		X		X
Lipid Profile Panel 1			X							X						X		
Lipid Profile Panel 2			X													X		
ESR ¹²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP ¹³	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology Profile			X													X		
Pharmacokinetic - TCZ			X ^{16c}							X ^{16c}						X ^{16c}		
Anti - TCZ Antibody			X ¹⁵							X ¹⁵						X ¹⁵	X ¹⁵	X ¹⁵
Sex Hormones			X							X						X		
Dipstick Urinalysis ¹⁴			X							X						X		
Infusions ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Corticosteroid Taper Per Guidance	X	X	X	X	X	X	X	X		X	X	X	X	X				

Primary Clinical Review
Reviewer: Nikolay P. Nikolov, M.D.
BLA 125,276, supplement 64
tocilizumab (Actemra)

TB = tuberculosis; CXR = chest X-ray; ECG = electrocardiogram; CHAQ = Childhood Health Assessment Questionnaire; JADI = Juvenile Arthritis Damage Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IL-6 = interleukin-6; sIL-6R = soluble interleukin-6 receptor; VAS = visual analogue scale; JIA ACR30 = juvenile idiopathic arthritis American College of Rheumatology 30

- ¹ The parent or patient (if the legal age of consent according to local standards) signed and dated an informed consent form before any study related activities could occur
- ² Medical history included information on prior immunization/vaccines
- ³ TB test was interpreted based on local guidelines for immunosuppressed patients (page 16218)
- ⁴ Chest radiograph could be utilized for screening purposes if obtained within 90 days prior to baseline. Required only if TB test positive or principal investigator indicated it was necessary to rule out infection or malignancy. TB test was repeated annually. Repeat chest radiograph was required if TB test converted to positive.
- ⁵ The Week 16 visit marked the last visit assessments for Part I, and the first infusion for Part II.
- ⁶ All assessments (safety, clinical, laboratory) except as noted were completed prior to start of infusion. If a severe infusion reaction felt to be anaphylactic or anaphylactoid nature was suspected, a blood sample for anti-TCZ antibodies was obtained.
- ⁷ JADI score consisted of 2 parts: Part A (articular) and Part E (extraarticular) each with separate score
- ⁸ Inactive disease in this study equated to no active joints, MD Global VAS \leq than 10 mm and ESR $<$ 20 mm (page 16211)
- ⁹ PA standard both wrists and hands (total 2 radiographs: one radiograph for combined L wrist and hand and one radiograph for R wrist and hand). Radiograph was optional (based on site decision) and was only to be obtained if site had requested and received Institutional Review Board/Independent Ethics Committee approval and written informed consent obtained from parent/guardian. It was obtained within 4 weeks following baseline and within \pm 4 weeks of other time points in Schedule of Assessments
- ¹⁰ Fasting laboratory tests after minimum 8-hour fast
- ¹¹ Urine pregnancy test for patients in Tanner stages \geq 2 or above only or after onset of menarche
- ¹² ESR done locally with furnished kits
- ¹³ CRP was not reported unblinded until Week 52
- ¹⁴ Dipstick urinalysis, pregnancy test on fresh voided urine sample
- ¹⁵ Pre-dose pharmacokinetic (TCZ concentrations) and pharmacodynamic (IL-6, and sIL-6R concentrations) were obtained from a single specimen obtained at indicated time points in Schedule of Assessments. Anti-TCZ antibodies were obtained from a separate specimen at indicated time points in Schedule of Assessments.
- ^{16a} Post-dose pharmacokinetic/ pharmacodynamic samples (obtained within 15 minutes following saline flush marking end of infusion) from opposite arm.
- ^{16b} Anytime of the day
- ^{16c} Only pharmacokinetic samples for TCZ
- ¹⁷ At screening 2 ECGs obtained 2 to 5 minutes apart
- ¹⁸ Focused physical examination (Examination could be limited to appropriate organ systems based on relevance to any ongoing adverse events), focused laboratory assessments could be appropriate depending on reason for discontinuation of study drug administration
- ¹⁹ W/D = Withdrawal visit – assessments were performed at the time of premature withdrawal from the study drug (ie, the patient had stopped study drug but agreed to complete the study including all withdrawal visits. No infusion was given at withdrawal visit. In all cases, the first withdrawal visit (Visit 33) was performed approximately 4 weeks after last infusion of study drug, followed by W/D2 assessments 4 weeks later, followed by W/D3 assessments 4 weeks later.
 - If a patient permanently discontinued study drug during Part 1 of the study (first \leq 16 weeks), no repeat of the wrist radiographs (X-rays) occurred at Visit 33.
 - If a patient permanently discontinued study drug during Part II of the study (Week 16 to Week \leq 40), repeat of the wrist radiographs (X-rays) occurred at Visit 33.
 - If a patient permanently discontinued study drug during Part III of the study ($>$ Week 40 to Week \leq 104), repeat of the wrist radiographs (X-rays) occurred at Visit 33 if more than 4 months had elapsed since previous wrist X-rays
- ²⁰ Chemistry included serum iron at baseline
- ²¹ Flare visit was designated when JIA ACR30 flare relative to Week 16 had occurred. At the first visit, when the flare definition was met, additional samples marked F were to be obtained but following the flare visit additional blood samples marked with flare were not to be obtained at subsequent visits. If flare occurred outside of defined study visits, unscheduled visit eCRF was used.

Source: CSR WA19977

Individual discontinuation rules for safety were mandated in the protocol as:

- Any reaction resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a significant decrease in blood pressure during or following study agent infusion
- Opportunistic infection
- Malignancy
- Pregnancy, positive pregnancy test or pregnancy planned within the study period or within 6 months after last study agent infusion
- The initiation of protocol prohibited medications
- Congestive heart failure
- Patient is deemed ineligible for the following TB criteria
 - A diagnosis of active TB is made
 - A patient receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with this therapy
 - A patient has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB and cannot or will not undergo additional evaluation
- A reaction suggestive of serum sickness and not representative of signs and symptoms of any other recognized clinical syndromes occurring up to 14 days following study agent administration. This reaction may result in myalgia and/or arthralgia with fever and/or rash that may be accompanied by other events including pruritis, facial, hand or lip edema, dysphagia, urticaria, sore-throat and headache.
- The investigator or Roche's medical monitor deems it is in the patient's best interest
- Any adverse event that in the opinion of the investigator or the sponsor precludes further study medication administration;
- Lack/loss of efficacy: Failure to maintain a JIA 30 at week 16 or for failure for three consecutive visits after week 12
- If three consecutive doses of study medication are missed due to abnormal liver enzyme tests (ALT, AST). Permanent discontinuation of study agent infusions must be considered for patients who develop a severe infusion reaction or serious infection. All patients who discontinue study agent infusions (but have not terminated study participation) will have all withdrawal visits, as specified in protocol section 5.4.3.

Section 7.1.4 of the protocol specified toxicity management guidelines with respect to blood chemistry abnormalities and hematology abnormalities that appear to be appropriate. For total bilirubin >3 mg/dl, dosing will be held, and repeat bilirubin and liver enzymes will be obtained in 1 week. If bilirubin persists >3 mg/dl, study medication will be permanently discontinued. If bilirubin returns to the normal range, study medication may be resumed. The liver enzyme abnormality management algorithm is described in Appendix 7 of the protocol, also appended below. If ANC is

less than 1000/mm³, dosing should be delayed and the lab repeated. If ANC is less than 500/mm³, the study drug should be permanently discontinued and the subject followed with safety visits to look for signs of infection until ANC >1500/mm³. If count does not return to >1500/mm³ by last WD4 safety visit a hematologic consult should be requested and subject followed till resolution or stabilization. If platelet count is less than 50,000/mm³, study medication dosing is to be delayed and the count repeated.

The protocol provided provisions for Data and Safety Monitoring Board (DSMB).

Efficacy Assessments

Primary endpoint:

Proportion of subjects who develop a JIA ACR30 flare (relative to week 16) from week 16 up to and including week 40 (Part II). JIA ACR30 flare is defined as 3 out of any 6 core outcome variables worsening by at least 30%, with no more than 1 of the remaining variables improved by more than 30% from week 16's evaluation and a minimum worsening of two active joints and at least 20 units on both subject's/parents and physicians global assessments on a scale from 0 to 100. JIA ACR response was derived from 6 variables:

- Parent/patient global assessment of overall well-being
- Physician global assessment of disease activity
- Number of joints with active arthritis
- Number of joints with limitation of movement
- ESR
- Functional ability determined by Childhood Health Assessment Questionnaire (CHAQ) disability index.

Key secondary efficacy assessments included:

- ACR JIA50, 70, 90 response rates
- ACR JIA components
- CRP concentration;
- Juvenile Arthritis Damage Index (JADI)
- Inactive disease status
- Juvenile Arthritis Disease Activity Score (JADAS)

Analysis populations:

- An intent-to-treat (ITT) population was defined to include all patients who were randomized into the lead-in phase and subsequently received at least 1 dose of TCZ. In addition an ITT population was defined for the Part I patients only (ie, those patients who participated in Part I), which was effectively the all ITT population. An ITT Part II population was also defined, this was the subset of patients from the ITT Part I who were subsequently randomized at Week 16

(beginning of Part II) to either placebo or TCZ. ITT treatment group allocation was as randomized at baseline and Week 16.

- Safety population: The overall Safety population includes all patients who were randomized into the lead-in phase study Part I and subsequently received at least one i.v. infusion of TCZ. For inclusion patients are also required to have had at least one post-Baseline assessment or event concerning safety (i.e. AEs, concomitant medications, laboratory data and vital signs). Analyses were performed with patients assigned to the TCZ treatment dose group which they first received at Baseline.
- A per-protocol (PP) population was defined based on the inclusion and exclusion criteria as assessed by medical review of the data, checks of timing of events etc., and monitor review at site. Patients that had events that were considered as potentially influencing the efficacy analysis were excluded from the PP population. The PP population was identified and finalized prior to unblinding of the patients' treatment.

Multiplicity Adjustments:

All statistical hypotheses for the primary and secondary endpoints were tested at the 5% significance level ($\alpha = 0.05$) using a 2-sided test. To control for the Type I error rate the secondary endpoints were tested in a hierarchical fixed sequence approach (see Table 62), if the primary endpoint was found to be statistically significant. Each endpoint in the sequence had to be significant ($p < 0.05$) in order for the subsequent endpoint in the chain to be considered significant.

Table 62. Hierarchical Fixed Sequence of Efficacy Endpoints in Study WA19977

Order No.	Primary Endpoint
1	Proportion of patients who develop a JIA ACR30 flare (relative to Week 16) in the period from Week 16 up to and including Week 40
	Secondary Endpoint
2	Proportion of patients with a JIA ACR30 response (relative to baseline) at Week 40
3	Proportion of patients with a JIA ACR50 response (relative to baseline) at Week 40
4	Proportion of patients with a JIA ACR70 response (relative to baseline) at Week 40
5	Change from baseline in number of joints with active arthritis at Week 40
6	Change from baseline in physician's global assessment of disease activity VAS at Week 40
7	Change from baseline in pain VAS at Week 40
8	Change from baseline in number of joints with limitation of movement at Week 40
9	Change from baseline in parent/patient's global assessment of overall well-being VAS at Week 40
10	Change from baseline in ESR at Week 40
11	Change from baseline in CHAQ-DI score at Week 40
12	Proportion of patients with a JIA ACR90 response (relative to baseline) at Week 40
13	Proportion of patients with inactive disease at Week 40

Source: CSR WA19977

Handling Missing Data:

- Missing data (missing at random or due to escaping post-flare) for the binary endpoints (JIA ACR flare, JIA ACR30/50/70/90, inactive disease, and time to flare) were considered as a worst case scenario of flared/non-responder.
- For continuous endpoints a last observation carried forward (LOCF) analysis was conducted, i.e. the JIA core components, the pain VAS, and the JADAS score. However, LOCF analysis did not consider further worsening of an endpoint beyond the point of flare if escape medication had not been taken, or if there would have been worsening of other JIA ACR components after the flare. Hence, caution is necessary when reviewing these outputs as the influence of patients flaring and moving to escape medication biased the results and there were considerably more flared patients in the placebo treatment group.

Sample Size Assumptions:

The primary endpoint of the study was a comparison (TCZ vs placebo) of the proportion of patients with JIA ACR30 flare in Part II. Patients had to have a JIA ACR30 response at the end of Part I (Week 16) in order to progress to Part II. This Part I JIA ACR30 response rate was anticipated to be 65% for the purpose of sample size calculations.

The sample size calculation assumed JIA ACR30 flare rates in Part II of 35% and 65% for the TCZ and placebo treatment groups, respectively. Sixty patients were required to be randomized to each group in Part II in order to achieve at least 80% power to detect a significant difference in the JIA ACR30 flare rates using a two-sided significance test with an $\alpha < 0.05$.

Under these assumptions, recruitment of 185 patients into Part I was deemed to provide the required number of patients needed in Part II.

9.4.1.2 Study WA19977: Conduct

This study followed the 'dual protocol approach' to accommodate the global nature of the study with investigator sites that cannot comply with investigational new drug (IND) requirements. The sponsor conducted the study with both an IND protocol (identified by the rest of the world [ROW] suffix) and an identical non-IND protocol (identified by the European Union [EU] suffix). The statistical assumptions and analyses were based on combined data from both protocols. The IND and non-IND protocol documents were updated identically throughout the study to maintain identical protocol documents. The protocol was conducted under a Special Protocol Agreement granted on June 08, 2009.

Study Dates:

Start date: October 14, 2009

Parts I and II are complete and included in this submission.

Part III is ongoing and the expected last-patient, last visit date is January 28, 2013

Protocol Amendments

The protocol was revised with Amendments B and C, submitted on October 16, 2009 and March 14, 2010, respectively which were minor, did not affect the protocol's substance and were considered acceptable under the existing SPA agreement. These amendments included the following changes:

- Updating and consolidation of Risk Mitigation Strategies to address safety issues seen with tocilizumab, including instructions that patients who experience serious hypersensitivity reaction that lead to a disruption of dosing are to be permanently discontinued from tocilizumab treatment.
- A number of changes to add clarity and clarification to the protocol.
- To include varicella zoster immunoglobulin, as this is commonly given to immunosuppressed children upon exposure to chicken pox if they have not already had chicken pox.
- Inclusion of an additional X-ray scoring method and related endpoints as exploratory endpoints.

- A test for latent TB was added at Week 100 to check for latent TB at the end of WA 19977 participation and enable ease of transition to local treatment with TCZ post WA19977.

Patient Disposition, Demographics, Efficacy and Safety are discussed in detail in the respective sections in this document.

9.4.2 Study MRA318JP

9.4.2.1 Study MRA318JP: Design

This was an open-label study conducted at five sites in Japan between November 2004 and July 2005. Patients were given three TCZ infusions of 8 mg/kg at 4-week intervals. The last observations were made at the week 12 visit, 4 weeks after the last infusion. The dose regimen and duration of treatment were based on the TCZ dosage regimen for RA in adults. In contrast to study WA19977, concomitant treatment with any DMARDs, including MTX, was not permitted. Further, changes to the dose were not permitted.

Patient Population:

The study enrolled patients 2 to 19 years of age who had been under 16 years of age at disease onset. Patients had to have a diagnosis of RF-positive or RF-negative polyarticular JIA or oligoarticular JIA according to the ILAR criteria.

Inclusion Criteria:

- Patients diagnosed as having RF-positive or RF-negative polyarticular JIA or oligoarticular JIA using the ILAR criteria (1997)
- Patients between 2 and 19 years of age
- Patients who were under 16 years of age at onset
- Patients who met all the following criteria at enrolment (within 2 weeks before the start of treatment with the investigational product)
 - Pain/tenderness and limited range of motion in 3 or more of the 74 joints examined
 - Inflammatory swelling in 5 or more of the 74 joints examined
 - ESR (Westergren method) \geq 30 mm/hr or CRP \geq 1.0 mg/dL
- Patients for whom written informed consent for participation in the study had been obtained from the parents (or legal guardian). (Written informed consent was also obtained from the patient personally if the patient had the necessary level of understanding.)

Exclusion Criteria:

- Patients assessed as having Class IV Steinbrocker functional activity at evaluation within 2 weeks before the start of treatment with the investigational product
- Patients treated with biological products (e.g., infliximab, etanercept) and leflunomide for the underlying disease within 12 weeks before the start of treatment with the investigational product
- Patients who received any of the following therapies within 2 weeks before the start of treatment with the investigational product
 - DMARDs or immunosuppressants
 - Intravenous, intra-articular or intramuscular injection of corticosteroids
 - Initiation or dose escalation of oral corticosteroids
 - Administration of oral corticosteroids exceeding 0.2 mg/kg as prednisolone equivalent (maximum 10 mg/day)
 - Surgical procedure (operation, etc.)
 - Plasmapheresis
- Patients with a WBC count less than 3500/ μ L (within 2 weeks before the start of treatment with the investigational product and before the 1st infusion of the investigational product)
- Patients with a neutrophil count less than 1000/ μ L (within 2 weeks before the start of treatment with the investigational product and before the 1st infusion of the investigational product)
- Patients with a platelet count less than 10×10^4 / μ L (within 2 weeks before the start of treatment with the investigational product and before the 1st infusion of the investigational product)
- Patients with a lymphocyte count less than 500/ μ L (within 2 weeks before the start of treatment with the investigational product and before the 1st infusion of the investigational product)
- ALT (GPT) 5-fold or more above the upper limit of the reference range for the study site (within 2 weeks before the start of treatment with the investigational product and before the 1st infusion of the investigational product)
- Total bilirubin 3-fold or more above the upper limit of the reference range for the study site (within 2 weeks before the start of treatment with the investigational product and before the 1st infusion of the investigational product)
- Patients with a history of serious allergy (e.g., shock, anaphylactoid symptoms)
- Patients who concurrently have any of the following serious diseases and who the investigator or subinvestigator concluded to be unsuitable as study subjects on medical grounds: Diseases of the circulatory system, blood and blood-forming organs, respiratory system, neuromuscular system, endocrine system, renal and urinary systems and digestive system
- Patients who had clear infection within 4 weeks before the start of treatment with the investigational product and who the investigator or subinvestigator concluded were unsuitable.

- Patients who participated in another clinical study within 6 months before the start of treatment with the investigational product
- Previously received MRA
- Women who were pregnant or lactating, who may have been pregnant or who were hoping to become pregnant during the study period
- Any other patients who the investigator or subinvestigator concluded were unsuitable as study subjects

Criteria for Individual Permanent Discontinuation:

- If the parents/legal guardian wanted the patient to be withdrawn from the study
- If a patient with the necessary level of understanding wished to be withdrawn from the study (Patients were generally considered to have the necessary level of understanding if they were a mature minor aged 15 years or over.)
- If the investigator or subinvestigator concluded that continued participation in the study was inappropriate due to the occurrence of an adverse event
- If the investigator or subinvestigator concluded that continued participation in the study was inappropriate due to the absence of any change in or exacerbation of symptoms (including changes in the method of treatment)
- If the appearance of anti-MRA antibodies was confirmed
- If the investigator or subinvestigator concluded that it would be difficult for the patient to continue participating in the study for some other reason

Criteria for Individual Temporary Discontinuation:

- ALT (GPT): Increase to 5-fold or more above the upper limit of the site reference range
- Total bilirubin: Increase to 3-fold or more above the upper limit of the site reference range
- WBC count: <2000/ μ L
- Neutrophil count: <1000/ μ L
- Lymphocyte count: <500/ μ L

Prior and Concomitant Therapy:

Concomitant use of the following drugs and therapy that it is believed would have affected the study was not permitted during the study.

- DMARDs and immunosuppressants (infliximab, etanercept, leflunomide, methotrexate, cyclosporin, sodium aurothiomalate, auranofin, D-penicillamine, lobenzarit disodium, bucillamine, actarit, salazosulfapyridine, mizoribine, azathioprine, etc.)
- Intravenous, intra-articular or intramuscular injection of corticosteroids
- Plasmapheresis
- Other drugs and treatment that may affect evaluation of drug efficacy (e.g., intra-articular injection of hyaluronates)
- Other investigational products

- Surgical procedure (operation, etc.). Acceptable if only a local procedure (tooth extraction, laser eye surgery, etc.).

The concomitant use of the following drugs and therapies was permitted. If these drugs or therapies were used concomitantly, however, all of the details (e.g., drug or therapy name, dosage regimen, duration [start date, continuation/completion date], reason for concomitant use) were to be entered on the case report form.

- The concomitant use of oral corticosteroids (≤ 0.2 mg/kg as prednisolone equivalent; maximum 10 mg/day) to treat JIA was permitted, but the dose was to remain the same.
- The concomitant use of NSAIDs was permitted, but concurrent use of two or more agents was forbidden. The addition of as-needed suppository use and mid-term switches to other NSAIDs was acceptable
- Topical corticosteroids
- Drugs to treat concurrent diseases could be used if it was believed that these would not affect evaluation of drug efficacy.

Study Monitoring:

Appears This Way On Original

Table 63. Schedule of Assessments in Study MRA318JP

	On enrolment ¹⁾	1st infusion			2nd infusion		3rd infusion			Last observation day
	≤2 wk	Wk 0 ²⁾	Wk 1	Wk 2	Wk 4 ²⁾	Wk 6	Wk 8 ²⁾	Wk 10	Wk 11	Wk 12
Treatment with the investigational product		●			●		●			
Patient baseline characteristics	●									
JIA core set		●			●		●			●
ECG	● ³⁾									
Chest X-ray	● ³⁾									
Height		●								●
Body weight		●			●		●			●
Blood pressure, pulse rate and body temperature		● ⁴⁾			● ⁴⁾		● ⁴⁾			
Haematology	● ⁵⁾	●		●	●	●	●	●		●
ESR	●	●			●		●			●
CRP	●	●		●	●	●	●	●	●	●
Blood chemistry	● ⁶⁾	●		●	●	●	●	●		●
Complement titre		●			●		●			●
Autoantibodies		●								●
Immunoglobulins		●								●
Serum amyloid A protein		●			●		●			●
Anti-MRA antibodies		●		●	●	●	●	●		●
Special tests		●			●		●		●	●
Serum MRA concentration		● ⁷⁾	●	●	●	●	●	●	●	●
Urinalysis 1		●			●		●			●
Urinalysis 2	●									●

Shaded cells: Centralised measurement (measured at (b) (4))

- 1) Conducted within 2 weeks before infusion of the investigational product (except ECG and chest X-ray).
- 2) Conducted the day before infusion of the investigational product or before infusion on the day of infusion
- 3) Conducted within 4 weeks before infusion of the investigational product.
- 4) Measured before infusion of the investigational product (day of infusion only) and at completion of infusion.
- 5) Only for the WBC count, neutrophil count, lymphocyte count and platelet count.
- 6) Only for ALT (GPT) and total bilirubin.
- 7) Conducted before starting infusion of the investigational product and 1 hour after completing infusion.

Source: CSR MRA318JP

Efficacy:

The primary efficacy endpoint:

JIA ACR30 response on the last observation day. A 30% improvement (ACR JIA30) was defined as at least 30% improvement in any three of the following six variables with no more than one of the remaining variables worsening by more than 30%. 50% improvement was defined as improvement of at least 50% in any three of the following six variables with no more than one of the remaining variables worsening by more than 30%. 70% improvement was defined in the same way. JIA core set

- Physician's global assessment for disease using a 10-cm visual analogue scale
- Parent/legal guardian or patient's global assessment for disease using a 10-cm visual analogue scale
- Functional assessment using the Japanese version of CHAQ
- Number of joints with active arthritis and number of joints with limited range of motion
- ESR

Secondary endpoints:

- Time courses of percentage of patients showing 30%, 50% and 70% improvement in the JIA core set up to the last observation day
- Time courses of the JIA core set components up to the last observation day
- Time course of CRP up to the last observation day
- Time course of pain up to the last observation day

Pharmacokinetic endpoints:

- Serum MRA concentration and
- Pharmacokinetic parameters (e.g., Cmax, time course of trough value, AUC, Kel, CL, Vd, Vdss, t1/2).

Handling of missing data:

Missing data were not imputed

Safety assessments:

The adverse events written in the case report form were converted using the MedDRA codes (Ver. 8.0), and the number of patients with adverse events and the number of adverse events were tabulated by SOC and PT. Adverse events for which a causal relationship could not be ruled out were treated as adverse drug reactions and the number of patients with these events and the number of these events were tabulated separately. The incidences and 95% confidence intervals for adverse events and adverse drug reactions were also determined. The time courses of the laboratory test values, etc., were examined based mainly on summaries of the data (descriptive statistics).

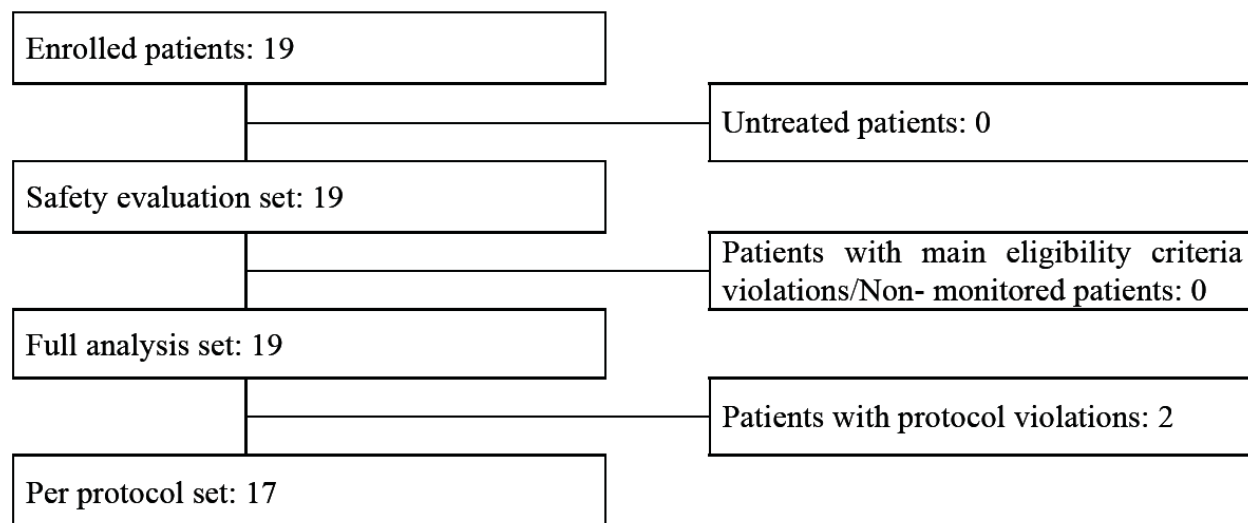
Analysis populations:

- Enrolled patient: Patients who were enrolled after the enrolment centre had checked the inclusion and exclusion criteria
- Safety evaluation set: Enrolled patients who were treated with the investigational product
- Full analysis set (FAS: maximum analysis population): Enrolled patients except “Untreated patients”, “Patients with main eligibility criteria violations/Non-monitored patients”
- Per protocol set (PPS: population complying with protocol): Patients in the FAS except “Patients with protocol violations”

9.4.2.2 Study MRA318JP: Conduct

Nineteen patients were enrolled in the study. In all 19 patients, the investigational product was administered three times as specified and the last observations were completed. None of the patients was withdrawn.

Figure 11. Patient Disposition in Study MRA318JP



Source: CSR MRA318JP

Patient Demographics and Disease Characteristics are presented in Section 6.1.2 Demographics above.

Efficacy for Study MRA318JP is discussed in Section 6 Review of Efficacy above.

Safety for Study MRA318JP is discussed in Section Review of Safety above.

9.4.3 Study MRA319JP

9.4.3.1 Study MRA319JP: Design

This was the long-term extension of study MRA318JP. The primary objective was to investigate the safety, efficacy, and pharmacokinetics of long-term treatment with TCZ for pJIA. Patients continued to receive open-label TCZ at a dose of 8 mg/kg q4w for at least one year after the first infusion in MRA318JP.

9.4.3.2 Study MRA319JP: Conduct

Of the 19 patients rolled over from study MRA318JP, four discontinued: one due to an AE (myasthenia gravis), one due to development of anti-TCZ antibodies before the 4th infusion without associated AEs or loss of efficacy, and two due to insufficient therapeutic response.

Patient Demographics and Disease Characteristics are presented in Section 6.1.2 Demographics above.

Efficacy for Study MRA319JP is discussed in Section 6 Review of Efficacy above.

Safety for Study MRA319JP is discussed in Section Review of Safety above.

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

/s/

NIKOLAY P NIKOLOV
03/22/2013

SARAH K YIM
03/25/2013

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125,276/64

Applicant: Hoffmann-LaRoche

Stamp Date: June 29, 2012

Drug Name: Tocilizumab

BLA Type: Supplemental

MO: Nikolay Nikolov, M.D.

On initial overview of the BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			-No new Product Quality, Pharm Tox, or Biopharmaceutics data
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			A single study provides efficacy data
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	The Application is a 505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			The Sponsor has conducted PK-PD relationship assessment in the pivotal study WA19977 and the supportive Japanese studies
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: WA19977 (under PREA)	X			The Sponsor provides one pivotal study to support the proposed indication

File name: 4_Clinical Filing Checklist for a sBLA 125276/64.0

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Indication: Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA) Pivotal Study #2: N.A.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	The pivotal study is multicenter international, and includes US sites
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Discussed as a Pre-sBLA meeting
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	These data were previously reviewed and found acceptable (Cardio-Renal Consult)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	These data were reviewed with the original BLA and found acceptable
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

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

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

File name: 4_Clinical Filing Checklist for a sBLA 125276/64.0

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	The pivotal study is multicenter international, and includes US sites
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. If submitting as a PDF document, include mapping in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 4_Clinical Filing Checklist for a sBLA 125276/64.0

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Nikolay P. Nikolov, M.D.	08/06/2012
Reviewing Medical Officer	Date
Keith Hull, M.D., Ph.D.	08/06/2012
Clinical Team Leader (Acting)	Date

Received: May 9, 2012
Filing Letter: August 28, 2012
PDUFA Goal: April 29, 2013

sBLA 125276/64 Tocilizumab for pJIA

MO: Nikolay Nikolov, M.D.
TL: Sarah Yim/Keith Hull, M.D.
Filing/Planning Meeting
August 6, 2012

1

sBLA Outline

- Sponsor: Hoffmann-LaRoche
- Product: Actemra®/tocilizumab (α IL-6R Mab)
- Approved indications:
 - Treatment of RA (01/08/2010 and 01/04/2011)
 - Treatment of sJIA (04/15/2011)
- Current sBLA intended indication:
 - Treatment of active pJIA in patients ≥ 2 years
- Efficacy study: WA19977 (SPA granted 6/8/09)
 - Part 1: 16-week TCZ lead-in period (n=188)
 - Part 2: 24-week DB, PC withdrawal period (n=166)
 - Part 3: 64-week OLE
- **Is the Application fileable: Yes**

2

Tocilizumab Experience

- Tocilizumab IV (Actemra®) has been extensively studied in both adults and children worldwide
 - RA, sJIA, pJIA, SLE
- Approved in the US:
 - RA, sJIA
- Approved in Japan:
 - Castleman's Disease, RA, sJIA, pJIA

3

Regulatory History

- **TCZ approved (01/08/10):** Signs and symptoms of RA
 - PREA requirement:
 - pJIA in children 2 to <18 years
 - FDA waived pediatric study requirements for ages 0 to <2 years
- **TCZ approved (04/15/11):** sJIA
- **New protocol submitted (10/2/09):** WA19977
- **SPA requested (11/17/08):** Granted with statistical changes (6/8/09)
 - Study WA19977
 - Part 1: 16-week TCZ lead-in period (n=188)
 - Part 2: 24-week DB, PC randomized withdrawal period (n=166)
 - Part 3: 64-week OLE up to 11/4/11
 - Supportive data from Chugai's pJIA program with data from 19 patients treated with TCZ for at least 1 year
- **Pre-sBLA meeting WR (05/01/12)**

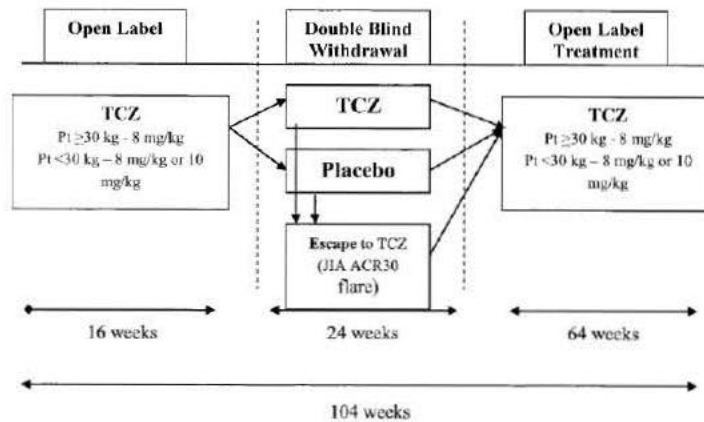
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Study WA19977 (SPA): Design

- Study population: 188 children
 - Ages 2-17 years
 - Active pJIA (RF+, RF-, extended oligoarticular JIA)
 - Inadequate response to MTX
- **Part I:** OL 16-week lead-in period, TCZ doses:
 - $\geq 30\text{kg}$: 8 mg/kg IV q4w
 - $< 30\text{kg}$: 8 or 10mg/kg IV q4w
- **Part II:** R (1:1), DB withdrawal for 24 weeks
- **Part III:** OLE of TCZ doses from Part I for 64 wks

5

Study Schema for WA19977



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Study WA19977: Endpoints

- 1° EP:
 - JIA ACR30 flare between weeks 16 and 40
- 2° EPs (hierarchical fixed sequence approach):
 - JIA ACR30/50/70/90 response rates, CFB
 - JIA core components, CFB
 - JADAS-27, CFB
 - Maintaining ACR response to week 40

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Summary of Efficacy

Endpoint	All Placebo N=81	All TCZ N=82	Difference ^a [95% CI]	p-value
Primary Efficacy Endpoint				
1 Proportion of patients with JIA ACR30 flare (relative to week 16): n (%)	39 (48.1%)	21 (25.6%)	-0.21 [-0.35;-0.08]	0.0024
Secondary Efficacy Endpoints				
2 Proportion of patients with JIA ACR30 Improvement: n (%)	44 (54.3%)	61 (74.4%)	0.19 [0.05; 0.33]	0.0084
3 Proportion of patients with JIA ACR50 Improvement: n (%)	42 (51.9%)	60 (73.2%)	0.20 [0.06; 0.34]	0.0050
4 Proportion of patients with JIA ACR70 Improvement: n (%)	34 (42.0%)	53 (64.6%)	0.22 [0.07; 0.37]	0.0032
5 CFB in number of active joints: Adjusted Mean	-11.4	-14.3	-2.9 [-5.7;-0.1]	0.0435
6 CFB in Physician's global assessments VAS: Adjusted Mean	-35.2	-45.2	-9.9 [-16.5;-3.4]	0.0031
7 CFB in the pain VAS: Adjusted Mean	-22.3	-32.4	-10.2 [-17.6;-2.7]	0.0076
8 CFB in number of joints with limitation of movement: Adjusted Mean	-7.7	-9.5	-1.8 [-4.1;0.5]	0.1229

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Exposure-Response

Table 2 Number (%) of Patients with JIA ACR Responses at Week 16 Following Treatment with Open-label TCZ (Study WA19977, Part 1)

	TCZ 10 mg/kg < 30 kg BW (N=35)	TCZ 8 mg/kg < 30 kg BW (N=34)	TCZ 8 mg/kg ≥ 30 kg BW (N=119)	All TCZ (N=188)
JIA ACR30, n (%)	31 (88.6)	26 (76.5)	111 (93.3)	168 (89.4)
JIA ACR50, n (%)	28 (80.0)	24 (70.6)	104 (87.4)	156 (83)
JIA ACR70, n (%)	22 (62.9)	14 (41.2)	81 (68.1)	117 (62.2)
JIA ACR90, n (%)	11 (31.4)	8 (23.5)	30 (25.2)	49 (26.1)

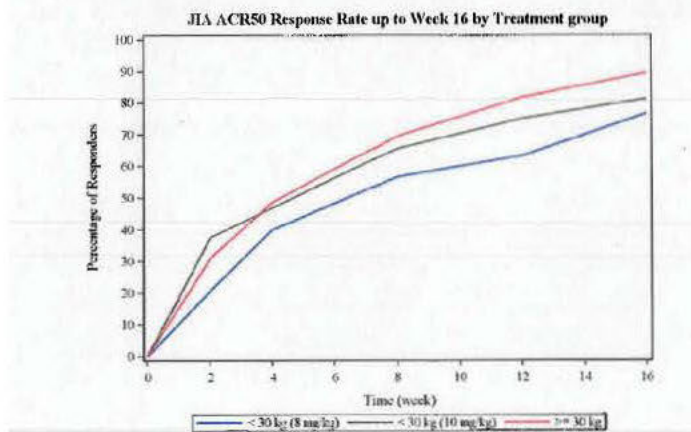
BW: body weight.

Patients who withdrew or for whom the endpoint could not be determined were classified as non-responders.

9

PK-Efficacy Relationship

Figure 5 JIA ACR50 and ACR70 Response Rate up to Week 16 (Study WA19977, Part 1)



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Summary of Safety

- Study WA19977
 - Part 1 complete (n=188)
 - Part 2 complete (n=166)
 - Part 3 ongoing (cutoff 11/4/11)
- Supportive safety/efficacy from Chugai's pJIA program
- Post Marketing Data
 - Japanese PMS Study ML21939 (n=179)
- Other data: SAEs for sJIA study WA18221

Study	Safety Population	Median Duration of Treatment	Patient Years of Exposure
<u>Pivotal phase III trial to evaluate efficacy and safety of TCZ in patients with pJIA:</u>			
WA19977 (TCZ all-exposure)	N = 188	0.9 years	184.4
<u>Supportive trials:</u>			
MRA318JP/MRA319JP	N = 19	3.2 years	55.7
ML21939 (JPMS)	N = 179	0.5 years	93.63

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Summary of Safety: Study WA19977

- No Deaths, No anaphylaxis
- 159/188 (85%) patients ≥ 1 AE
- 17/188 (9%) patients ≥ 1 SAE
 - 61% of SAEs and AEs were infections (9 serious, 1 TB)
- 22/29 patients withdrew in part 1 (15/22 due to inefficacy)
 - 5/29 withdrew due an AE
 - Sclerosing cholangitis, serum sickness-like reaction, benign intracranial hypertension, pneumonia, and abnormal bilirubin concentration

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Japanese Studies

Study	Study Design	TCZ Doses	Primary endpoint	Secondary endpoints
MRA318JP	12 week OL study of TCZ in 19 patients with oligoarticular, RF-positive and RF-negative pJIA	8mg/kg IV q4 wks	JIA ACR30 @ last observation: 94.7%	JIA ACR50: 94.7% JIA ACR70: 57.9%
MRA319JP	≥1 year extension study of MRA318JP (median treatment time 3 years)	8mg/kg IV q4w	JIA ACR30 @ week 24: 94.1%	JIA ACR50: 94.1% JIA ACR70: 94.1% <i>In 16 patients who completed 24 wks of treatment</i>

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Japanese studies Summary of Safety:

- MRA318JP (12 week)
 - 3 SAEs:
 - 2 Gastroenteritis, 1 sensory disturbance
 - Adverse events
 - Infections and infestations: 11/19 patients (57.9%)
- MRA319JP (LT extension of MRA318JP)
 - 6 SAEs:
 - Gastroenteritis, influenza, pneumonia, myasthenia gravis, bacterial gastroenteritis, sensory disturbance
 - Adverse events
 - Infections and infestations: 18/19 patients (94.7%)
 - 60 events

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Brief Review of Labeling

- Indication:
 - Actemra is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in pediatric patients 2 years of age and older”
 - Dosing:
 - 8 mg/kg IV q4wk in pediatric patients weighing ≥ 30 kg
 - 10 mg/kg IV q4wk in pediatric patients weighing < 30 kg
- Section 14, Clinical Studies, proposed:

(b) (4)

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Approved Therapies for pJIA

- **Etanercept**
 - Enbrel is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older.
- **Adalimumab**
 - Humira is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older. Humira can be used as monotherapy or concomitantly with MTX.
- **Abatacept**
 - Orencia is indicated for reducing signs and symptoms in pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. Orencia may be used as monotherapy or concomitantly with MTX.

The sBLA proposed labeling of Actemra is generally consistent with the labeling of the already approved products for pJIA above

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Tocilizumab REMS

- **REMS approved 1/8/10**
 - Included:
 - Medication guide, communication plan, & timetable for submission of assessments (18 mo, 3 and 7 yrs)
 - REMS modifications:
 - Medication guide removed (3/23/11)
 - Proposal incorporating sJIA (4/5/11)
 - 18-month assessment (7/7/11)
 - REMS modification notification sent (9/12/11)
 - Proposed REMS modification (11/11/11 and 2/3/12)
 - Prescriber re-education slide deck
- **This supplement**
 - Update the Actemra REMS with the pJIA indication
 - Re-send “Dear Healthcare Provider Letter” with updated indication
 - Prescribing Information highlight differences in dose between pJIA, RA, and sJIA

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Conclusions and Mid-Cycle Deliverables

- **Application is fileable, as a Standard sBLA**
 - Clinical filing checklist complete: no omissions, one comment
- **Advisory Committee: Not recommended**
- **Mid-cycle deliverables: Complete review of:**
 1. Study WA19977 as a pivotal efficacy and dose-selection study
 2. Studies MRA318PJ and MRA319JP as pivotal dose-selection studies
 3. Efficacy EPs proposed for labeling
 4. **Safety:**
 - SAE, SIE
 - Adverse Events of Interest:
 - Laboratory abnormalities (Lipids, Hepatic)
 - GI perforations
 - Immunogenicity

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Other Disciplines

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/s/

NIKOLAY P NIKOLOV
08/07/2012

KEITH M HULL
08/07/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

ENVIRONMENTAL ASSESSMENT



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 24, 2013

From: Gerald M. Feldman, Ph.D.
Laboratory of Molecular and Developmental Immunology
Division of Monoclonal Antibodies, CDER

Subject: BLA 125276.64: Categorical Exclusion for Environmental Assessment

Through: Marjorie Shapiro, PhD, Chief, LMDI, DMA, OBP, CDER.

To: BLA 125276.64 FILE

Sponsor: Hoffmann-La Roche Inc.

Contact: Kristine Ogozalek, Assoc Director, Drug Regulatory Affairs
973-235-6227

Date Submitted: June 28, 2012
PDUFA Deadline: April 29, 2013

This supplement is to expand the indication of tocilizumab (Actemra) for the treatment of patients 2 years of age and older who are suffering from polyarticular Juvenile Idiopathic Arthritis (pJIA).

A categorical exclusion has been submitted under 21 CFR § 25.31(c). The applicant avers (Section 1.12.14 of the current submission) that the proposed action is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action or that would warrant the submission of additional environmental information.

Reviewer's Comment:

The Sponsor's claim of categorical exemption is acceptable.

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/s/

GERALD M FELDMAN
03/19/2013

MARJORIE A SHAPIRO
03/20/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125276Orig1s064

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: BLA 125276, Supplement 64
[ACTEMRA[®] (tocilizumab)]

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Division of Pulmonary, Allergy, and Rheumatology Products
Pharmacology and Toxicology Team Leader

DATE: April 1, 2013

The purpose of this supplement dated June 28, 2012 was to provide data in support of the use of ACTEMRA at the doses of 10 mg/kg for patients <30 kg and 8 mg/kg for patients ≥30 kg given once every 4 weeks for following indication: ACTEMRA[®] (tocilizumab) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

No nonclinical pharmacology or toxicology studies were provided in this supplement dated June 28, 2012. No labeling changes are needed in nonclinical sections of the product label. See Dr. Mukherjee's Filing Review.

As there are no outstanding pharmacology/toxicology issues for this BLA Supplement, the BLA Supplement is recommended for approval from the nonclinical perspective.

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/s/

TIMOTHY W ROBISON
04/01/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: sBLA STN 125276
supplement# 64

Drug Name: ACTEMRA® (tocilizumab)

Indication(s): For the treatment of active Polyarticular Juvenile Idiopathic Arthritis (pJIA) in patients 2 years of age and older

Applicant: Hoffmann-La Roche, Inc.

Date(s): Submitted: June 28, 2012
PDUFA: April 29, 2013

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Yongman Kim, Ph.D.

Concurring Reviewers: Joan Buenconsejo, Ph.D.

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

Clinical Team: Nikolay Nikolov, M.D.
Sarah Yim, M.D.

Project Manager: Philantha Bowen

Keywords: Clinical studies, pediatric trial, sensitivity analyses

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1. EXECUTIVE SUMMARY

Hoffmann-La Roche, Inc. provided data from study WA19977 to support the use of tocilizumab (TCZ, hereafter) at the doses of 10 mg/kg for patients weighing less than 30 kg and 8 mg/kg for patients weighing at least 30 kg given once every 4 weeks to treat active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older. Based on my review of the data and study report, the study provided a robust data supporting the efficacy of tocilizumab meeting the pre-specified study success criterion: superiority of tocilizumab to placebo in terms of JIA American College of Rheumatology (ACR) 30 flare.

The major efficacy findings are as follows:

1. A statistically significantly lower proportion of patients in the TCZ group had JIA ACR30 flare compared to placebo.
2. A greater improvement from baseline in number of active joints in the TCZ group was achieved at Week 40 compared to the placebo group.
3. A greater improvement from baseline in Physician's global assessments in the TCZ group was achieved at Week 40 compared to the placebo group.
4. A greater improvement from baseline in the pain VAS in the TCZ group was achieved at Week 40 compared to the placebo group.

I conclude that the evidence of efficacy from the study is substantial and robust in terms of missing data handling though judged not important due to limited number of patients with missing data and in terms of subpopulations based on study region, baseline demographic characteristics and background concurrent treatment.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Tocilizumab (TCZ), previously referred to as myeloma receptor antibody (MRA), is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against the soluble and membrane bound interleukin 6 receptor (IL-6R).

In 2010, tocilizumab was approved for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonists. Then in 2011, tocilizumab was approved for the treatment of active sJIA in patients two years of age or older.

The current submission is seeking for approval of tocilizumab in treating active pJIA in patients 2 years of age and older.

2.1.2 History of Drug Development and Regulatory Interactions

The following are chronological study milestones with regulatory interactions:

- IND meeting held (20 March 2007)
- Special Protocol Assessment (SPA) agreed (8 June 2009)
- Study started (14 October 2009)
- Data cut-off for primary analysis (4 November 2011)
- Statistical Analysis Plan (SAP) finalized (12 December 2011)
- Database locked (16 December 2011)
- Pre-sBLA written response sent (9 May 2012)
- sBLA submitted (28 June 2012)

In accordance with the Pediatric Research Equity Act of 2003, the applicant submitted this sBLA to fulfill the requirement from the original Actemra BLA submission dated December 20, 2007 and the BLA approval letter on January 8, 2010 as the “REQUIRED PEDIATRIC ASSESSMENT” for the indication of Rheumatoid Arthritis.

In addition, the applicant noted that the pediatric study requirement for ages 0 to < 2 years for pJIA was waived as necessary studies are impossible or highly impracticable.

In the IND meeting in 2007, the pediatric clinical development program for pJIA was discussed between the applicant and the Division. The Division provided the applicant with advices on the draft protocol synopsis for pJIA. Subsequently, in 2008, the applicant submitted Protocol WA19977 to the Division for SPA. Several issues were raised by the Division including issues with the analysis plan; therefore, the Division did not enter into SPA agreement at that time.

In 2009, the applicant submitted another request for SPA. In that submission, the applicant addressed the issues raised by the Division in 2008. Stratification and statistical analysis concerns were addressed by reducing the number of stratification factors of background MTX use and corticosteroid use. Also, the handling of missing values for continuous secondary endpoints was addressed by applying last observation carried forward (LOCF) imputation and multiplicity concern was addressed by using a fixed sequence of endpoints. Further, we agreed with the approach to handle missing data for the primary endpoint, that is, patients who withdrew (for any reason) or who took escape medication will be assigned as ‘flared.’ Although we previously agreed in applying LOCF to impute missing data, this is not something we will agree now. We will not agree to a single-value imputation that assumes patients’ scores at the time of drop out will be the same at the end of the study, particularly when the reason for dropout is treatment-related. Nonetheless, since only about 4% of all patients withdrew during double-blind withdrawal phase, the concern on LOCF imputation on the analyses was not warranted.

We also agreed that results of study, if positive, would support a sBLA filing for the indication of pJIA.

2.1.3 Specific Study Reviewed

The focus of this statistics review is on a single Phase 3 study WA19977. The study is a 2-year, randomized withdrawal, double-blind, placebo-controlled, multi-national, multi-center trial. There were 58 participating investigational sites: 4 sites in Argentina, 2 sites in Australia, 2 sites in Belgium, 4 sites in Brazil, 4 sites in Canada, 4 sites in France, 4 sites in Germany, 4 sites in Italy, 4 sites in Mexico, 3 sites in Peru, 5 sites in Poland, 6 sites in Russian Federation, 2 sites in Spain, 3 sites in the United Kingdom, 7 sites in the United States.

2.1.4 Major Statistical Issues

Following is a list of noteworthy statistical issues I focused in my review:

1. Robustness of efficacy data – analysis sets, missing data, subsets by center, subgroups by demographic characteristics, subgroups by baseline background treatments, secondary outcomes, statistical analysis models, covariates (randomization stratified by background MTX use and corticosteroid use)
2. Multiplicity adjustment for secondary endpoints.

These issues will be discussed further in the sections 3.2, 4.1, 4.2, and 5.1.

2.2 Data Sources

sBLA 125276 was submitted on June 28, 2012 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report including protocols, statistical analysis plan, and all referenced literature can be found in the EDR. SAS codes used in statistical analyses and the electronic SAS data sets with raw and derived variables and data definitions were provided in the EDR using the following path:

[\\cbsap58\mleCTD Submissions\STN125276\125276.enx](#)

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data are acceptable in terms of quality and integrity. I was able to reproduce the primary and key secondary efficacy analyses. No noticeable deviations between

CRFs and analysis datasets relevant to primary and key secondary endpoints were found. Also I verified the randomized treatment assignments.

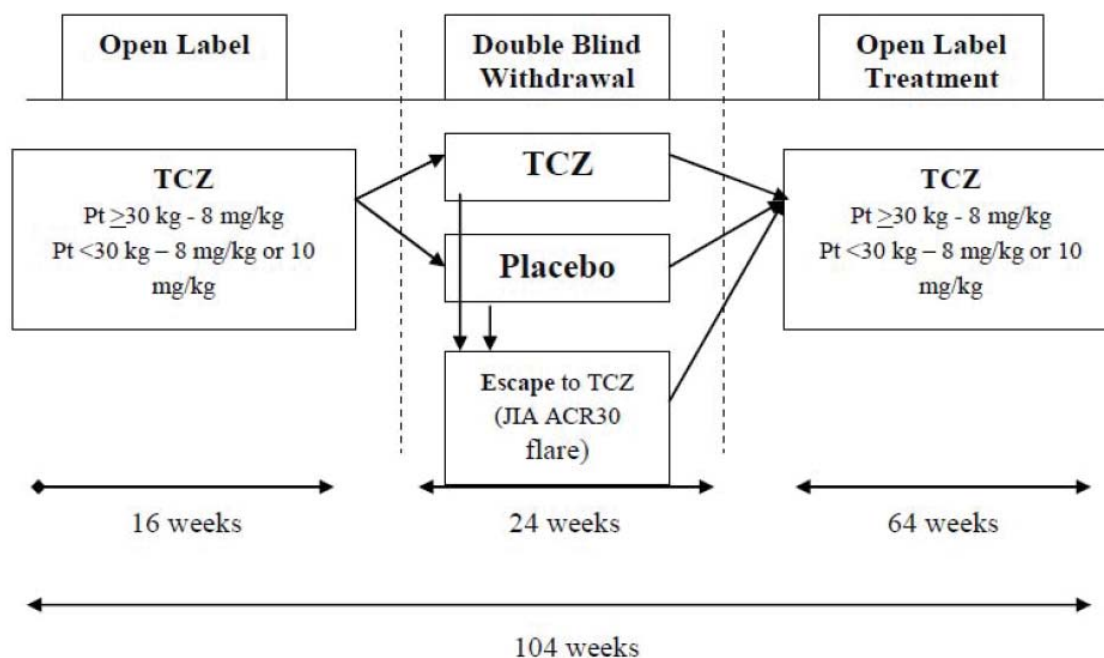
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study WA19977 employed randomized, multi-center, placebo-controlled, parallel-group, double-blind, and withdrawal design. The study consists of three phases (Figure 1): 16 weeks of active tocilizumab treatment lead-in phase (or Phase 1), 24 weeks of double-blind randomized withdrawal phase (or Phase 2), and 64 weeks of open-label extension phase (or Phase 3).

In phase 1, patients weighing < 30 kg were randomized in 1:1 to either TCZ 8 mg/kg or 10 mg/kg IV infusion and patients weighing \geq 30 kg were given TCZ 8 mg/kg IV infusion. In phase 2, responders based on JIA ACR30 at Week 16 in phase 1 were randomized to tocilizumab or placebo in 1:1 ratio stratified by background MTX use and corticosteroid use. This is then followed by a 64-week open-label extension where everyone who remained in the study will be taking tocilizumab.

Figure 1: Study Design



Source: Adapted from the statistical analysis plan, figure 1 (page 12).

The primary endpoint was the proportion of patients who developed a Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology (ACR) 30 flare (relative to Week 16) in

study phase 2 (i.e. by Week 40). JIA ACR30 flare was defined as three of six core outcome variables worsening by at least 30%, with no more than one of the remaining variables improved by more than 30% since the week 16 evaluation and a minimum worsening of two active joints and at least 20 units on both subject's/parents and physicians global assessments on a scale from 0 to 100.

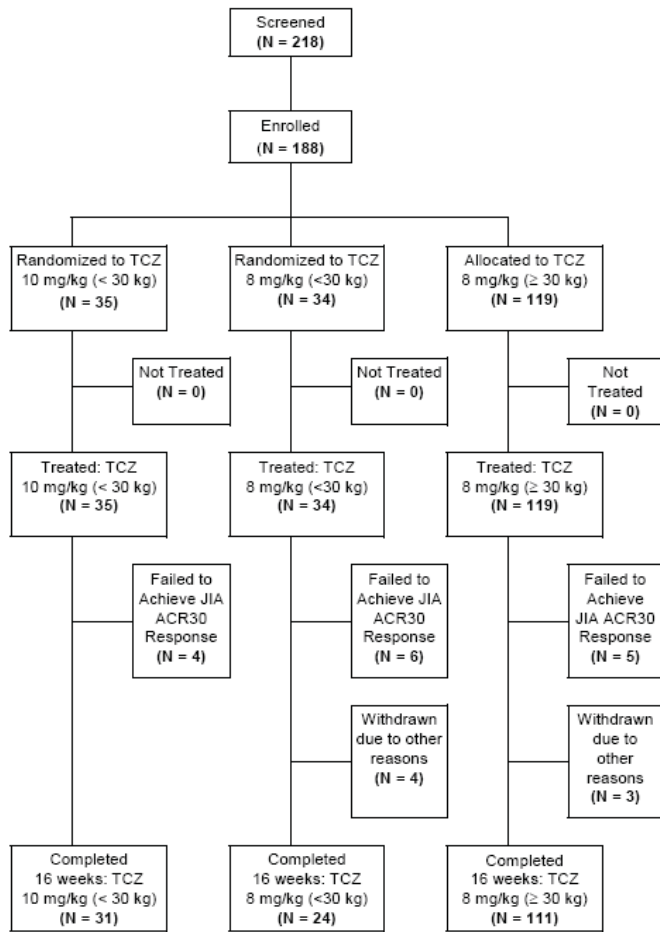
Secondary endpoints with multiplicity adjustment plan included proportion of patients with JIA ACR30/50/70/90 responses at Week 40, change from baseline (CFB) in the JIA ACR core components at Week 40, CFB in the pain visual analogue scale (VAS) at Week 40, CFB in the Physician's global assessment at Week 40, CFB in the Patient/parent's global assessment at Week 40, CFB in number of active joints at Week 40, CFB in number of joints with limitation of movement at Week 40, CFB in ESR at Week 40, CFB in CHAQ-DI score at Week 40, proportion of patients with inactive disease at Week 40. Therefore, other analyses than primary analysis and secondary analyses specified above are to be treated as exploratory from a regulatory perspective and are discouraged to be included in the label.

Study seemed to be conducted properly based on the submission when I assessed the history of regulatory interactions, protocol revisions/amendments, study report, study datasets, and internal consistency among those components.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

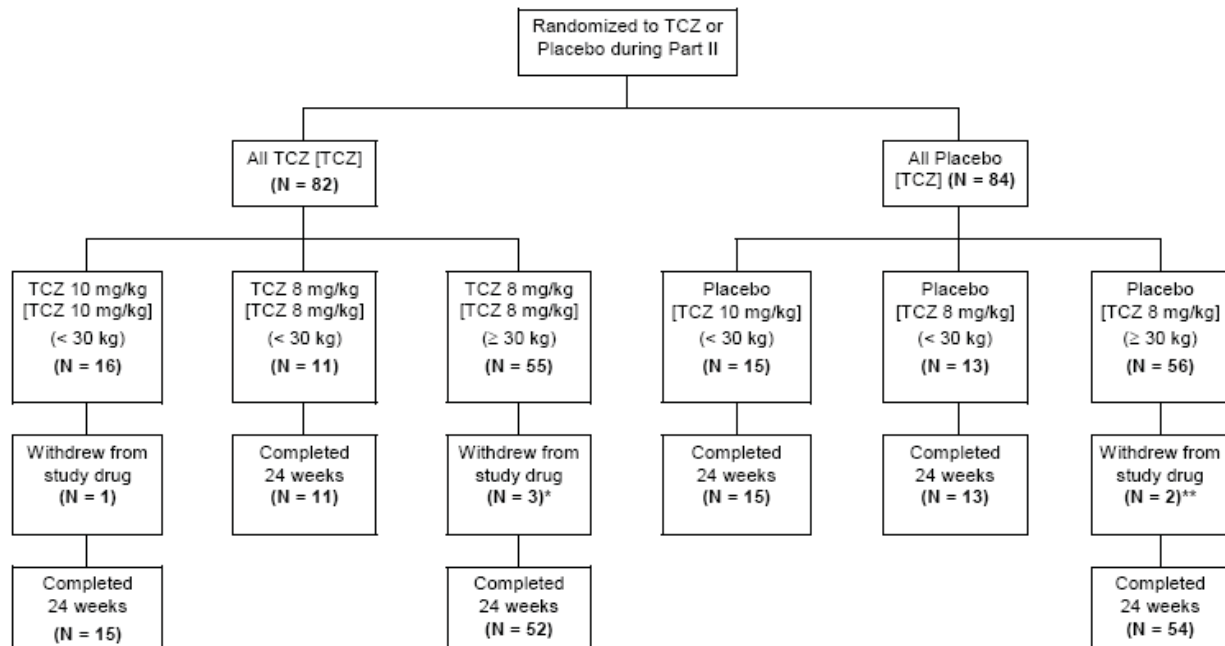
Patients enrolled in the study were aged 2 years up to and including age 17 years with at least 6 months active pJIA with an inadequate response to methotrexate, due to lack of efficacy or toxicity, who were receiving standard of care, either with or without non-steroidal anti-inflammatory drugs (NSAIDs), either with or without or low-dose corticosteroids, and either with or without concomitant methotrexate therapy. A total of 188 patients were enrolled into the study and treated with tocilizumab in phase 1 with 63% (119 patients) weighing at least 30 kg. Of the 166 patients who completed phase 1, 163 patients were randomized and took study medication in phase 2. About 67% of patients weighed at least 30 kg in each treatment arm. The following charts describe the patient disposition during phase 1 (Figure 2) and phase 2 (Figure 3).

Figure 2: Patient Disposition during Phase 1



Source: Adapted from the clinical study report, figure 1 (page 85).

Figure 3: Patient Disposition during Phase 2



Source: Adapted from the clinical study report, figure 2 (page 86).

Following are my findings regarding disposition from the database and these are consistent with the Applicant's report.

- Phase 1 (OL) :
 - 188 entered
 - 166 (88%) completed & 22 (12%) withdrew (15 due to LOE, 3 AE, & 4 other)
- Phase 2 (DB):
 - 165 were randomized to placebo (82) or TCZ (83)
 - 163 (99%) took study medication (81 placebo & 82 TCZ)
 - 156 (96%) completed (77 placebo & 79 TCZ)
 - 7 (4%) withdrew (4 placebo & 3 TCZ)
 - 2 due to AE (1 placebo & 1 TCZ)
 - 55 (34%) escaped (36 placebo & 19 TCZ)

The primary efficacy analysis was conducted on the intent-to-treat (ITT) population. The ITT set included all randomized patients in phase 2 who took at least one study drug (n=163).

There were no noticeable imbalances of the demographics and baseline characteristics between treatment groups (Table 1).

Overall, the average age of patients was 11 years, 77% female, 80% Caucasian, 79% concurrent MTX user, 46% corticosteroid user, and the average disease duration was 4 years. The average weight of those who weighed < 30 kg was about 21 kg, and the average weight of those who weighed at least 30 kg was about 50 kg.

Table 1: Baseline Demographic and Medical Characteristics

	TCZ 10 mg/kg (< 30 kg) (N = 35)	TCZ 8 mg/kg (< 30 kg) (N = 34)	TCZ 8 mg/kg (≥ 30 kg) (N = 119)	All TCZ (N = 188)
Age (years), mean (SD)	6.9 (3.02)	7.6 (2.71)	13.1 (2.78)	11.0 (4.01)
Females, n (%)	30 (86)	24 (71)	90 (76)	144 (77)
White Race, n (%)	28 (80)	28 (82)	94 (79)	150 (80)
Non-Hispanic Ethnicity, n (%)	22 (63)	23 (68)	80 (67)	125 (66)
Weight (kg), mean (SD)	20.7 (5.7)	22.4 (5.3)	50.0 (12.6)	39.6 (17.3)
Height (cm), mean (SD)	117.1 (15.3)	120.4 (14.1)	153.7 (13.7)	140.8 (22.0)
Body surface area (m ²), mean (SD)	0.8 (0.17)	0.9 (0.16)	1.5 (0.22)	1.2 (0.36)
Disease duration (years), mean (SD)	3.4 (2.39)	3.5 (2.57)	4.7 (4.16)	4.2 (3.67)
Prior DMARDs use, n (%)	21 (60)	26 (76)	87 (73)	134 (71)
Prior biologics use, n (%)	8 (23)	6 (18)	47 (39)	61 (32)
Number of Joints with Active Arthritis, mean (SD)	23.9 (18.3)	21.2 (13.6)	18.9 (13.0)	20.3 (14.3)
Number of Joints with LOM, mean (SD)	23.1 (19.2)	17.3 (13.3)	16.0 (12.7)	17.6 (14.4)
Patient/Parent Global Assessment VAS, mean (SD)	51.5 (26.9)	59.1 (26.2)	51.6 (24.1)	52.9 (25.0)
Physician Global Assessment VAS, mean (SD)	64.7 (20.5)	64.7 (18.5)	59.4 (21.3)	61.4 (20.7)
CHAQ-DI Score, mean (SD)	1.7 (0.71)	1.8 (0.68)	1.2 (0.69)	1.4 (0.74)
ESR, mean (SD)	35.1 (24.1)	36.6 (23.0)	34.2 (26.7)	34.8 (25.5)
Concurrent Methotrexate Use, n (%)	29 (83)	30 (88)	89 (75)	148 (79)
Median Dose mg/m ² /week	14.3	14.1	11.4	11.8
Corticosteroid Use, n (%)	15 (43)	18 (53)	54 (45)	87 (46)
Average Dose (mg/kg/day) (SD)	0.15 (0.033)	0.15 (0.038)	0.12 (0.052)	0.13 (0.048)

Source: Adapted from the clinical study report, table 7 (page 90).

3.2.3 Statistical Methodologies

The Cochran-Mantel-Haenszel (CMH) test was used in the analysis of dichotomous endpoints including the primary JIA ACR30 flare and other secondary JIA ACR30/50/70/90 adjusting for the stratification factors of background MTX use (yes or no) and corticosteroid use (yes or no) applied at randomization. A logistic regression analysis was also conducted to see how consistent the parametric regression analysis was with the non-parametric analysis.

The analysis of covariance (ANCOVA) was used in the analysis of change from baseline of continuous endpoints including pain VAS adjusting for the stratification factors of background MTX use and corticosteroid use applied at randomization. The baseline value of the continuous variables was included as a covariate.

Time to event (days) of the dichotomous flare/responder endpoints was summarized using Kaplan-Meier estimates and a log-rank test was used to determine if there is a difference between the TCZ and placebo groups. Patients who discontinued the treatment or escaped due to flare were treated as censored.

To control for the type I error rate, the secondary endpoints were tested in a hierarchical fixed sequence approach. Each endpoint in the sequence must be significant ($p < 0.05$) in order for the subsequent endpoint in the chain to be considered significant (Table 2).

Table 2: Hierarchical Testing Procedure

Order No.	Primary Endpoint
1	Proportion of patients who develop a JIA ACR30 flare (relative to Week 16) in the period from Week 16 up to and including Week 40
Secondary Endpoints	
2	Proportion of patients with a JIA ACR30 response (relative to Baseline) at Week 40
3	Proportion of patients with a JIA ACR50 response (relative to Baseline) at Week 40
4	Proportion of patients with a JIA ACR70 response (relative to Baseline) at Week 40
5	CFB in number of joints with active arthritis at Week 40
6	CFB in physician's global assessment of disease activity VAS at Week 40
7	CFB in pain VAS at Week 40
8	CFB in number of joints with limitation of movement at Week 40
9	CFB in parent/patient's global assessment of overall well-being VAS at Week 40
10	CFB in ESR at Week 40
11	CFB in CHAQ-DI score at Week 40
12	Proportion of patients with a JIA ACR90 response (relative to Baseline) at Week 40
13	Proportion of patients with inactive disease at Week 40

Source: Adapted from the statistical analysis plan, table 1 (page 20).

To handle missing data in the primary analysis, patients who withdrew (for any reason) or who took escape medication were assigned as 'flared.' This approach was accepted via SPA agreement. A sensitivity analysis treating those patients as 'non-flared' was conducted by the applicant. For the continuous missing ACR core components, LOCF was used. This approach was also accepted via SPA agreement. Although we previously agreed in applying LOCF to impute missing data, this is not something we will agree now. We will not agree to a single-value imputation that assumes patients' scores at the time of drop out will be the same at the end of the study. Nonetheless, since only about 4% of all patients withdrew during double-blind withdrawal phase, the concern on LOCF imputation on the analyses was not warranted.

The applicant conducted several subgroup analyses based on demographics and baseline characteristics – age group (≤ 7 , 8-12, ≥ 13), sex, background MTX use (yes, no), corticosteroid use (yes, no). I added a subgroup analysis based on race (white, non-white).

The applicant also conducted the study with an IND protocol in non-European Union (EU) region and with an identical non-IND protocol in EU region, while stating that the data would be analyzed in aggregate. To assess internal consistency among region (EU or non-EU), I conducted a subset analysis by region after combining sites within each region.

3.2.4 Results and Conclusions

In this presentation of the results, I focused on the data from the 24 weeks of double-blind withdrawal phase in the submission and presented descriptive analyses on the 16 weeks of active lead-in phase.

The single efficacy study WA19977 met the criteria for the study success: superiority of tocilizumab to placebo in terms of JIA ACR30 flare rates (Table 3). A statistically significant difference was also observed when patients who withdrew from treatment were assigned as having not flared. I agree that the 12 patients who were randomized at Week 16 but withdrew or took escape medication prior to Week 40 without experiencing a JIA ACR30 flare were not influential in determining the treatment effect. Further, result from parametric analysis using logistic regression was also consistent with the result from the non-parametric CMH analysis (Table 4). Kaplan-Meier analysis and log-rank test were conducted on the time to JIA Flare by the applicant (Figure 4). Two curves of time to JIA ACR30 flare were statistically separated favoring TCZ over placebo.

Table 3: JIA ACR30 Flare Rates (CMH Analyses on ITT Population)

	N	n	Flare Rate	Weighted Difference [†] vs. PBO (95% CI)	P-value
Primary Analysis (Reviewer)					
TCZ	82	21	26 %	-22 % (-35%, -8%)	.0024
PBO	81	39	48 %		
Sensitivity Analysis (Applicant)#					
TCZ	82	14	17 %	-24 % (-36%, -11%)	.0003
PBO	81	34	42 %		

[†]Weighted difference & its CI calculated from the algorithm by Ge, Durham, et.al. (Drug Information Journal, Vol. 45, pp 481-493, 2011). See appendix for the algorithm adapted from the article.

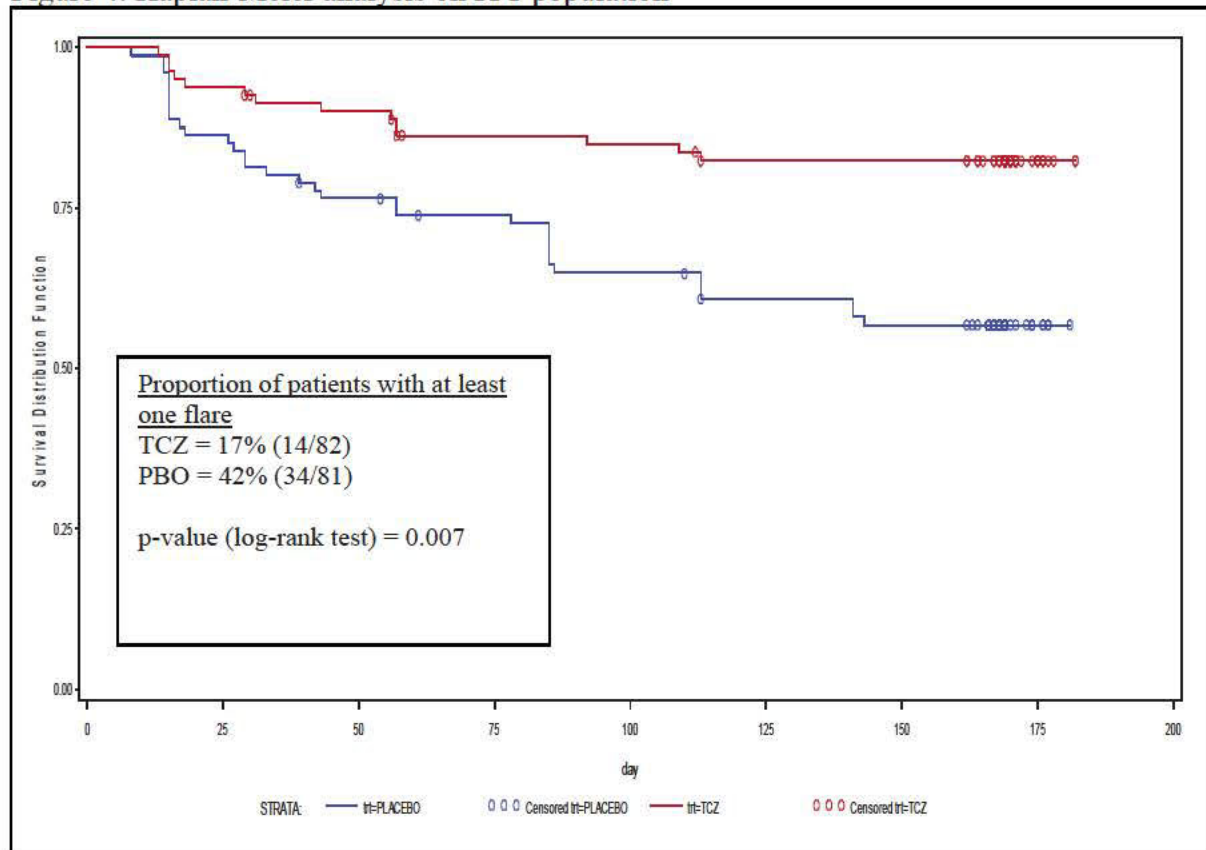
#Source: Adapted from the clinical study report (page 421)

Table 4: Logistic Regression Analysis on ITT Population

	Odds Ratio	95% CI for Odds Ratio	P-value
N=163			
Treatment Comparison (reference = PBO, n = 81)			
TCZ, n=83	0.35	(0.17, 0.71)	.0035
Background MTX Use Comparison (reference = Yes, n = 130)			
No, n=33	6.08	(2.51, 14.72)	<.0001
Background Corticosteroid Use Comparison (reference = No, n = 92)			
Yes, n=71	1.75	(0.85, 3.60)	.1259

Source: Adapted from the clinical study report (page 423).

Figure 4: Kaplan-Meier analysis on ITT population



Although I was not able to exactly reproduce the applicant's results from the analyses of secondary endpoints (Appendix, Table 11), my summary on the secondary endpoints analyses is consistent with the applicant's conclusion (Table 5 & Table 6).

- A higher proportion of patients in the tocilizumab arm achieved JIA ACR/30/50/70 improvement at Week 40 compared with the placebo arm.
- A greater change from baseline in number of active joints in the tocilizumab arm achieved at Week 40 compared with the placebo arm.
- A greater change from baseline in Physician's global assessments in the tocilizumab arm achieved at Week 40 compared with the placebo arm.
- A greater change from baseline in the pain VAS in the tocilizumab arm achieved at Week 40 compared with the placebo arm.
- A numerically greater change from baseline in number of joints with limitation of movement in the tocilizumab arm achieved at Week 40 compared with the placebo arm. Since the difference was not statistically significant, the sequential test stopped with this endpoint.

Table 5: Secondary Efficacy Endpoints Analyses (Reviewer's)

	N	n	Response Rate	Weighted Difference† vs. PBO (95% CI)	P-value
JIA ACR30					
TCZ	82	61	74 %	19 % (5%, 33%)	.0084
PBO	81	44	53 %		
JIA ACR50					
TCZ	82	60	73 %	20 % (6%, 34%)	.0050
PBO	81	42	52 %		
JIA ACR70					
TCZ	82	53	65 %	22 % (7%, 37%)	.0032
PBO	81	34	42 %		

†Weighted difference & its CI calculated from the algorithm by Ge, Durham, et.al. (Drug Information Journal, Vol. 45, pp 481-493, 2011). See appendix for the algorithm adapted from the article.

Table 6: Secondary Efficacy Endpoints Analyses (Reviewer's)

Treatment	N	LS Mean† Change from Baseline at Week 40	Difference vs. PBO		
			LS Mean† Difference	95% CI	P-value
Active Joint Count					
TCZ	82	-14.2	-2.9	(-5.8, -0.1)	.0436
PBO	81	-11.3			
Physician's Global Assessment					
TCZ	82	-43.7	-9.1	(-15.9, -2.3)	.0091
PBO	81	-34.6			
Pain VAS					
TCZ	82	-31.6	-9.6	(-17.1, -2.0)	.0131
PBO	81	-22.0			
Joints with Limitation of Movement					
TCZ	82	-9.4	-1.9	(-4.2, 0.3)	.0948
PBO	81	-7.5			
Patient/Parent Global Assessment					
TCZ	82	-31.9	-7.3	(-14.7, -0.0)	(.0512)‡
PBO	81	-24.6			
ESR					
TCZ	82	-25.1	-13.7	(-19.1, -8.2)	(<.0001)‡
PBO	81	-11.4			
CHAQ-DI					
TCZ	82	-0.8	-0.2	(-0.4, -0.0)	(.0257)‡
PBO	81	-0.6			

†LS Means calculated from ANCOVA model with terms for treatment adjusting for background MTX use, corticosteroid use, and baseline score as covariate.

‡Due to non-significance of joints with LOM in hierarchical test procedure, these p-values were considered nominal.

Since two doses of tocilizumab – 8mg/kg for patients weighing > 30 kg & half of patients weighing ≤ 30 kg and 10mg/kg for half of patients weighing ≤ 30 kg were given during the double blind phase, the descriptive analysis comparing those two doses were conducted (Table 7). It appears that there is a smaller rate of flare in 10mg/kg group compared to 8mg/kg group, but this could be due to small sample size.

Table 7: JIA ACR30 Flare Rate (TCZ 8mg versus 10mg)

Treatment	N	n	Flare Rate	Difference vs. PBO
PBO	81	39	48 %	
TCZ 8 mg/kg	66	18	27%	-21 %
TCZ 10mg/kg	16	3	19 %	-29 %

3.3 Evaluation of Safety

The assessment of the safety aspects of the study drug was mainly conducted by reviewing medical team, Drs Nikolov and Yim.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In addition to standard subgroup analyses based on patient demographics, I included subgroup analyses by region to see if there is any significant inconsistency of efficacy among regions and by baseline background treatment use.

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were conducted by demographic variables of sex, age group, and race (Table 8). Each subgroup by demographics showed that there seems no noticeable interaction between treatment and demographic factors except for race. The interaction, however, is possibly due to small sample size of non-white patients.

Table 8: Reviewer's subgroup analysis by demographics

	Sex	N	n	Flare Rate	Difference vs. PBO
Female					
	PBO	62	30	48 %	
	TCZ	66	18	27 %	-21 %
Male					
	PBO	19	9	47 %	
	TCZ	16	3	19 %	-26 %
Age					
≤7					
	PBO	15	6	40 %	
	TCZ	14	2	14 %	-26 %
8-12					
	PBO	35	16	46 %	
	TCZ	40	12	30 %	-16 %
≥13					
	PBO	31	17	55 %	
	TCZ	28	7	25 %	-30 %
Race					
White					
	PBO	64	33	52 %	
	TCZ	65	15	23 %	-29 %
Non-White					
	PBO	17	6	35 %	
	TCZ	17	6	35 %	0 %

A subset analysis was conducted by geographic region to see if there was any noticeable difference in flare between regions noting that study was conducted in EU under non-IND protocol and in non-EU under an identical IND protocol. Each subgroup by region showed that there seems an effect favoring TCZ in each region. The treatment effect, however, seems mainly to be driven from EU sites (Table 9).

Table 9: Reviewer’s subset analysis by study region (EU or Non-EU)

Treatment	N	n	Flare Rate	Difference vs. PBO
EU				
PBO	46	24	52 %	
TCZ	41	7	17 %	-35 %
Non-EU				
PBO	35	15	43 %	
TCZ	41	14	34 %	-9 %

4.2 Other Special/Subgroup Populations

The following analyses are the subgroup analyses by baseline characteristics, particularly, the use of background therapy of methotrexate or corticosteroid. Patients with background MTX treatment had less flare rates when compared to patients without background MTX treatment. However, there seems no significant interaction between the MTX use and treatment effect in terms of flare. Similar conclusion could be drawn regarding the concurrent oral corticosteroid use.

Table 10: The applicant’s subgroup analysis by Background MTX use and by Corticosteroid use

Treatment	N	n	ACR30 Flare Rate at Week 40	Difference vs. PBO	Treatment by background MTX (corticosteroid) interaction test p-value*
Background MTX use at Baseline = Yes					
PBO	64	25	39%		
TCZ	67	13	19%	-20%	
Background MTX use at Baseline = No					
PBO	17	14	82%		
TCZ	15	8	53%	-29%	0.3980
Background oral corticosteroid use at Baseline = Yes					
PBO	38	21	55%		
TCZ	33	8	24%	-31%	
Background oral corticosteroid use at Baseline = No					
PBO	43	18	42%		
TCZ	49	13	27 %	-15 %	0.3670

*P-values calculated from logistic regression with terms for treatment, background MTX (corticosteroid), and treatment-by-background MTX (corticosteroid) interaction.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

During the review of the clinical study, several statistical issues that warrant further exploration of data and discussion in the review were identified. The impact of missing data was not prominent because missing binary endpoints such as JIA ACR30 were treated conservatively using non-responder imputation. Missing continuous endpoints including JIA ARC core components were imputed by the last observation carried forward (LOCF). Since only about 4 percent of all patients - 4 patients from TCZ and 3 patients from placebo - withdrew during double-blind withdrawal phase, the concern on LOCF imputation on the analyses was not important. The proposed multiplicity adjustment method properly controlled type-1 error rate in the analyses of the secondary endpoints.

5.2 Comments on the proposed label

Following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the study description and primary analysis results and their interpretation. I had minor edits such as deletion of decimals and changing proportions to percents. I added the definition of JIA ACR30 Flare. All changes I made were highlighted in yellow color.

Polyarticular Juvenile Idiopathic Arthritis

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 28 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. [Module 2.5 section 1.3.1.1](#); [Module 5.3.5.1 WA19977 CSR section 3.4](#); [Module 2.7.3 section 2.1.1.2, Table 4](#).

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 Part I (b) (4) of patients 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 (b) (4)%, and (b) (4)%, respectively. Module 5.3.5.1 WA19977 CSR section 3.1 & section 4.1; Module 2.7.3 section 2.1.2.2.1, Table 7.

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. Module 5.3.5.1 WA19977 CSR section 3.1 & section 4.1.

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR30 flare was defined as 3 (b) (4) 6 core outcome variables worsening by at least 30%, with no more than 1 of the remaining variables (b) (4) by more than 30% (b) (4) Week 16.

ACTEMRA treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] vs 48% [39/81]; adjusted difference in (b) (4) -21%, 95% CI: -35%, -8%). Module 2.7.3 section 2.1.2.1, Table 6.

During the withdrawal phase (Part II), (b) (4) (u) (4) Module 2.7.3 section 2.1.2.3.2, Table 14.

(b) (4)

5.3 Conclusions and Recommendations

In my opinion, the study provided a robust data supporting the efficacy of tocilizumab meeting the pre-specified study success criterion: superiority of tocilizumab to placebo in terms of JIA ACR30 flare.

The major efficacy findings are as follows:

1. A statistically significantly lower proportion of patients in the TCZ group had JIA ACR30 flare compared to placebo.
2. A greater improvement from baseline in number of active joints in the TCZ group was achieved at Week 40 compared to the placebo group.

3. A greater improvement from baseline in Physician's global assessments in the TCZ group was achieved at Week 40 compared to the placebo group.
4. A greater improvement from baseline in the pain VAS in the TCZ group was achieved at Week 40 compared to the placebo group.

I conclude that the evidence of efficacy from the study is substantial and robust in terms of missing data handling though judged not important due to number of patients with missing data and in terms of subpopulations based on study region, baseline demographic characteristics and background concurrent treatment.

APPENDICES

Table 11: Applicant's Hierarchical Analysis of Significance Testing on Efficacy Endpoints

	Endpoint	All Placebo N=81	All TCZ N=82	p-value
Primary Endpoint				
1	Proportion with JIA ACR30 flare (relative to Week 16)	39 (48.1%)	21 (25.6%)	0.0024
Secondary Endpoints				
2	Proportion of patients with JIA ACR30 Improvement Number (%)	44 (54.3%)	61 (74.4%)	0.0084
3	Proportion of patients with JIA ACR50 Improvement Number (%)	42 (51.9%)	60 (73.2%)	0.0050
4	Proportion of patients with JIA ACR70 Improvement Number (%)	34 (42.0%)	53 (64.6%)	0.0032
5	Change from baseline in number of active joints Adjusted Mean	-11.4	-14.3	0.0435
6	Change from baseline in Physician's global assessments VAS Adjusted Mean	-35.2	-45.2	0.0031
7	Change from Baseline in the Pain VAS Adjusted Mean	-22.3	-32.4	0.0076
8	Change from baseline in number of joints with limitation of movement, Adjusted Mean	-7.7	-9.5	0.1229
9	Patient/parent global assessment VAS Adjusted Mean	-24.7	-32.1	*****
10	Change from baseline in ESR (mm/hr) Adjusted Mean	-12.0	-26.3	*****
11	CHAQ-DI score	-0.6	-0.8	*****
12	Proportion with JIA ACR90 improvement Number (%)	19 (23.5%)	37 (45.1%)	*****
13	Proportion with Inactive Disease Number (%)	12 (14.8%)	26 (31.7%)	*****

***** p-values for these variables are not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity

Source: Adapted from the clinical study report (page 95).

Algorithm for CMH weighted difference & its variance by Ge, Durham, et.al. (Drug Information Journal, Vol. 45, pp 481-493, 2011):

The CMH method is a weighted average across strata of the stratum-specific difference in proportions. Let n_{ti} and n_{ci} denote the number of treated and control subjects in stratum i , and P_{ti} , \hat{P}_{ti} , P_{ci} , and \hat{P}_{ci} denote the population and observed proportions of responders in the treated and control groups in stratum i respectively. The CMH weight for stratum i weight is $w_i = n_{ti}n_{ci}/(n_{ti} + n_{ci})$, and the estimated risk difference and its variance are:

$$\hat{d} = (\sum_i w_i (\hat{P}_{ti} - \hat{P}_{ci})) / (\sum_i w_i)$$

$$\text{var}(\hat{d}) = (\sum_i w_i^2 \text{var}(P_{ti} - P_{ci})) / (\sum_i w_i)^2.$$

where

$$\begin{aligned} \text{var}(\hat{P}_{ti} - \hat{P}_{ci}) &= (P_{ti}(1 - P_{ti})/n_{ti} + P_{ci}(1 - P_{ci})/n_{ci}) \\ &= (\hat{P}_{ti}(1 - \hat{P}_{ti})/n_{ti} + \hat{P}_{ci}(1 - \hat{P}_{ci})/n_{ci}). \end{aligned}$$

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Yongman Kim, Ph.D.

Date: March 19, 2013

Concurring Reviewer(s): Joan Buenconsejo, Ph.D.

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

/s/

YONGMAN KIM
03/19/2013

JOAN K BUENCONSEJO
03/20/2013
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: sBLA 125276 Applicant: Hoffmann-La Roche Stamp Date: 6/28/2012

**Drug Name: Actemra NDA/BLA Type: sBLA
(tocilizumab)**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			Assessed by clinical team
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Yongman Kim	8/7/2012
Reviewing Statistician	Date
Joan Buenconsejo	8/7/2012
Supervisor/Team Leader	Date

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

/s/

YONGMAN KIM
08/07/2012

JOAN K BUENCONSEJO
08/07/2012
I concur

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125276Orig1s064

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

CLINICAL PHARMACOLOGY REVIEW

BLA	125276/064
Submission Date:	06/28/2012
Brand Name	ACTEMRA®
Submission Type	Efficacy Supplement
Generic Name	Tocilizumab
OCP Reviewer	Liang Zhao, Ph.D.
Team Leader (Acting)	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Pulmonary, Allergy and Rheumatology Products (DPARP)
Sponsor	Hoffmana-La Roche Inc.
Formulation; Strength(s); Administration Route	Single-use vials of ACTEMRA (20 mg per mL) (i.e., 80 mg per 4 mL, 200 mg per 10 mL, or 400 mg per 20 mL); A single intravenous drip infusion over 1 hour.....
Approved Indication	Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies and treatment of pediatric patients with active systemic juvenile idiopathic arthritis in patients 2 years and older
Proposed Indication	Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.
Approved Dosage Regimen	Rheumatoid arthritis (RA) Recommended adult dosage every 4 weeks: Patients who have had an inadequate response to one or more TNF antagonists. When used in combination with DMARDs or as monotherapy, the recommended starting dose is 4 mg per kg followed by an increase to 8 mg per kg based on clinical response. Systemic juvenile idiopathic arthritis (sJIA) Recommended SJIA dosage every 2 weeks: 12 mg per kg for patients less than 30 kg weight 8 mg per kg for Patients at or above 30 kg weight
Proposed Dosage Regimen	Polyarticular Juvenile Idiopathic Arthritis (pJIA) Recommended adult dosage every 4 weeks: 10 mg per kg for patients less than 30 kg weight 8 mg per kg for Patients at or above 30 kg weight

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1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Summary statistics for the PK parameters calculated from the serum tocilizumab (TCZ) concentrations for pivotal study WA19977 along with sponsor estimated results using population PK modeling and simulation were reported as follows: For doses of 8 mg/kg TCZ (patients weighing ≥ 30 kg) given every 4 weeks, the predicted mean (\pm SD) $AUC_{wk12-16}$, C_{max} and C_{min} of TCZ were 1231 ± 361 mcg \cdot day/mL, 182 ± 37 mcg/mL and 7.49 ± 8.2 mcg/mL, respectively. For doses of 10 mg/kg tocilizumab (patients weighing < 30 kg) given every 4 weeks, the predicted mean (\pm SD) $AUC_{wk12-16}$, C_{max} and C_{min} of TCZ were 968 ± 254 mcg \cdot day/mL, 175 ± 32 mcg/mL and 2.35 ± 3.59 mcg/mL, respectively. The estimated accumulation ratios were 1.05 and 1.16 for AUC_{4weeks} , and 1.43 and 2.22 for C_{min} for 10 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) doses, respectively. No accumulation for C_{max} was observed. Because of the dependence of total clearance on TCZ serum concentrations, the half life of tocilizumab is also concentration dependent and cannot be reported with a universal value.

Body size as measured by BSA was found to be the most influential covariate for the linear part of and the overall clearance, central volume of distribution, and peripheral volume of distribution. The proposed dose is based on another measure of body size, the body weight, which should be highly correlated to BSA. Therefore, the body weight based dosing strategy by matching PK exposure for different body weight groups is reasonable.

The impact of immunogenicity on PK exposure, efficacy, and/or safety remains inconclusive for pJIA population given its low incidence (n=1 in pivotal study WA19977) and the relatively small database.

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Chemistry and Physico-Chemical Properties: Tocilizumab (RO4877533, TCZ) is a humanized anti-human IL-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass produced using recombinant DNA technology.

The tocilizumab molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulfide linkages. The Molecular formula for TCZ is $C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$ (polypeptide moiety only).

TCZ has a molecular weight of approximately 149 kDa (146 kDa protein plus 3 kDa carbohydrate).

Formulation: Tocilizumab is supplied as a sterile liquid concentrate for solution for intravenous (iv) infusion available at a concentration of 20 mg/mL.

2.1.2. What is the approved therapeutic indication, dosage and route of administration?

Indication:

Rheumatoid Arthritis (RA)

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Systemic Juvenile Idiopathic Arthritis (sJIA)

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

Dosage and Route of Administration:

Rheumatoid Arthritis

Recommended Adult Dosage Every 4 Weeks	
Patients who have had an inadequate response to one or more TNF antagonists	When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg followed by an increase to 8 mg per kg based on clinical response.

Systemic Juvenile Idiopathic Arthritis

Recommended 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

2.2 General Clinical Pharmacology

2.2.1. What are the clinical pharmacology and clinical trials used to support the proposed claims?

This submission is primarily based on one pivotal phase III clinical trial in patients with pJIA (protocol WA19977). In addition, supportive data are available from two phase III trials conducted by Chugai in Japan and one study from the Japanese postmarketing surveillance (JPMS) program. All these studies are listed in Table 1.

Table 1. Overview of Clinical Data on TCZ in pJIA Patients.

Study	Design	Patients
Pivotal phase III trial to evaluate efficacy and safety of TCZ in patients with pJIA:		
WA19977	Two-year study in three parts: <u>Part I</u> : 16-week open-label TCZ therapy: BW ≥ 30 kg: 8 mg/kg TCZ IV q4w BW < 30 kg: 8 or 10 mg/kg TCZ IV q4w <u>Part II</u> : 24-week double-blind, placebo-controlled, randomized withdrawal period in patients achieving JIA ACR30 response at week 16 of Part I; same TCZ dose as in Part I or placebo <u>Part III</u> : 64-week open-label extension (ongoing)	Patients with pJIA for at least six months and with at least five active joints; age at screening was 2-17 years. Treated in <u>Part I</u> : N = 188 (8 mg/kg TCZ: n = 153; 10 mg/kg TCZ: n = 35) Treated in <u>Part II</u> : N = 163 (8 mg/kg TCZ: n = 66; 10 mg/kg TCZ: n = 16; placebo: n = 81)
Supportive trials:		
MRA318JP	12-week open-label, single-arm study; TCZ dose 8 mg/kg IV q4w	Japanese patients with pJIA with at least five active joints; age at baseline 3-19 years; N = 19
MRA319JP	Long-term extension of MRA318JP; total TCZ 8 mg/kg IV q4w treatment duration 0.35–3.53 years	Patients who completed MRA318JP: N = 19
ML21939 (JPMS)	6-month observational cohort study in Japan	pJIA patients: N = 179

BW: body weight.

2.2.2. Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Serum concentrations of TCZ were determined by a validated enzyme-linked immunosorbent assay (ELISA) (b) (4)

The assay precision of quality control samples (CV%) ranged from 10.9% to 16.5%. The overall accuracy ranged from 104.3% to 107.9%. The assay sensitivity in terms of LLOQ (lower limit of quantitation) was 100 ng/mL for TCZ (concentration in native serum) and 2.50 ng/mL for TCZ (concentration in assay).

2.2.3. What are the PK characteristics of TCZ in pJIA patients?

Summary statistics for the PK parameters calculated from the serum TCZ concentrations at the first and third infusions for study MRA318JP are shown in Table 2. The $t_{1/2}$ values for the first and third infusions, 123 ± 41.5 hours vs 130 ± 50.6 hours were comparable (CSR for MRA318JP). It was found that TCZ exposure decreased with body weight. As shown in Table 3 based on model predictions, following four infusions of 8 mg/kg (≥ 30 kg) and 10 mg/kg (< 30 kg) every 4 weeks in pJIA patients, C_{max} values are comparable to those in RA patients following 8 mg/kg infusion given every 4 weeks at steady state (182 and 175 $\mu\text{g/mL}$ vs. 187 $\mu\text{g/mL}$). C_{min} for 8 mg/kg infusion given every 4 weeks in pJIA patients is comparable to the C_{min} in RA patients following 8 mg/kg IV once every 4 weeks (7.5 $\mu\text{g/mL}$ vs. 8.6 $\mu\text{g/mL}$) at body weight of >30 kg.

Table 2. Summary statistics for PK parameters following first and third infusions in pJIA patients (based on Study MRA318JP)

PK Parameter	Units	N	Mean±SD	Median	Min	Max
First Infusion						
AUC _{inf}	µg·hour/mL	12	25300±6720	24300	12300	37000
AUC _{last}	µg·hour/mL	19	20700±7130	21100	10400	33500
CL	mL/hour/kg	12	0.342±0.112	0.329	0.219	0.641
C _{max}	µg/mL	19	145±37.4	136	95.5	217
t _{1/2}	hour	12	123±41.5	107	76.0	208
k _{el}	1/hour	12	0.00617±0.00176	0.006450	0.00330	0.00910
MRT	hour	12	178±46.0	166	132	278
T _{max}	hour	19	5.52±8.12	2.67	2.08	29.1
V _{dss}	mL/kg	12	58.3±13.9	56.6	40.8	84.6
V _d	mL/kg	12	56.9±13.4	55.4	39.3	87.2
Third infusion						
kel	1/hour	11	0.00589±0.00173	0.00620	0.00270	0.00810
t _{1/2}	hour	11	130±50.6	112	86.0	256

Source: CSR for MRA318JP; Blood sampling day deviated by more than ±3 days from the scheduled blood sampling day (7 and 14 days from the immediately preceding infusion day).

Table 3. Model predicted PK exposure parameters for pJIA and sJIA pediatric patients and in adults RA

Population	Dose Regimen	C _{max} , µg/mL	C _{min} , µg/mL	AUC _{2weeks} , µg·day/mL	AUC _{4weeks} , µg·day/mL
sJIA	8 mg/kg Q2W (≥30 kg)	226±54.5	54.5±20.7	1337±409	NA
	12 mg/kg Q2W (<30 kg)	263±54.1	60.5±25.5	1346±426	NA
pJIA Japanese	8 mg/kg Q4W	145±34.7	4.88±4.68 (week 12)	NA	1054±280 (AUC _{inf} for first dose)
pJIA	8 mg/kg Q4W (≥30kg)	182±37	7.49±8.20	NA	1231±361
	10 mg/kg Q4W (<30kg)	175±32	2.35±3.59	NA	968±254
	8 mg/kg Q4W (<30kg)	140±25	0.95±2.37	NA	702±218
RA	8 mg/kg Q4W	187±85	8.6±8.9	NA	1417±613
	4 mg/kg Q4W	88±41	1.4±1.9	NA	538±239

Mean±SD is reported. Q2W=every 2 weeks; Q4W= every 4 weeks; NA=not applicable. All PK parameters were PK model computed parameter except for pJIA Japanese where non-compartmental analysis was used.

Summary statistics for the PK parameters calculated from the serum TCZ concentrations for pivotal study WA19977 along with sponsor predicted results using population PK modeling and simulation were shown in Tables 4 & 5. For doses of 8 mg/kg tocilizumab (patients weighing >= 30 kg) given every 4 weeks, the predicted mean (± SD) AUC_{wk12-16}, C_{max} and C_{min} of TCZ were 1231 ± 361 mcg·day/mL, 182 ± 37 mcg/mL and 7.49 ± 8.2 mcg/mL, respectively. For doses of 10 mg/kg tocilizumab (patients weighing < 30 kg) given every 4 weeks, the predicted mean (± SD) AUC_{wk12-16}, C_{max} and C_{min} of TCZ were 968 ±254 mcg·day/mL, 175 ± 32 mcg/mL and 2.35 ± 3.59 mcg/mL, respectively. The predicted accumulation ratios were 1.05 and 1.16 for

AUC_{4weeks}, and 1.43 and 2.22 for C_{min} for 10 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) doses, respectively. No accumulation for C_{max} was observed. Because of the dependence of total clearance on TCZ serum concentrations, the half life of tocilizumab is also concentration dependent and cannot be reported with a universal value.

Table 4. Summary of TCZ pharmacokinetic exposure parameters to week 16 by treatment group (Part I)

PK Parameters	TCZ 10 mg/kg (< 30 kg)	TCZ 8 mg/kg (< 30 kg)	TCZ 8 mg/kg (≥ 30 kg)
Model Computed	n = 32	n = 30	n = 115
AUC _{wk12-16} , µg·day/mL	968±254 (934, 445-1658)	702±218 (712, 336-1239)	1231±361 (1157, 610-2228)
C _{max_wk12} , µg/mL	175±32 (175,108-256)	140±25 (141, 92-187)	182±37 (179,107-341)
C _{min_wk16} , µg/mL	2.35±3.59 (0.88, 0-16.3)	0.95±2.07 (0.09, 0.0-7.7)	7.49±8.20 (4.11, 0.0-36.3)
Observed	n = 29	n = 27	n = 113
C _{wk16}	2.75±4.19 (1.02, 0.0-18.7)	0.98±2.26 (0.0, 0.0-9.06)	7.44±8.48 (4.4, 0.0-39.1)

Table 5. Summary of TCZ pharmacokinetic exposure parameters to week 40 by treatment group (Part I and II)

PK Parameters	TCZ 10 mg/kg (< 30 kg)	TCZ 8 mg/kg (< 30 kg)	TCZ 8 mg/kg (≥ 30 kg)
Model Computed	n=12	n=11	n=50
AUC _{wk36-40} , µg·day/mL	1204±341 (1113, 822–2132)	853±208 (857, 498–1202)	1417±482 (1287, 656–2885)
C _{max_wk36} , µg/mL	201±43 (191, 153–312)	155±24 (160, 118–190)	198±47 (201,113–341)
C _{min_wk40} , µg/mL	5.34±6.80 (3.20, 0.0–21.2)	3.14±5.96 (0.33, 0.0–20.1)	9.60±9.59 (7.29, 0.0–32.3)
Observed	n=11	n=11	n=50
C _{trough}	4.12±4.38 (2.20, 0.2–15.0)	2.03±3.30 (0.45, 0.0–10.8)	9.71±9.40 (6.83, 0.0–33.2)

2.2.4. What are the PD characteristics of tocilizumab in patients?

Levels of sIL-6R increased rapidly at Week 1 and remained high thereafter (MRA318JP and WA19977). Within each dosing interval, levels of sIL-6R increased post infusion and then decreased prior to the next infusion. The pattern is more prominent for patients in the 8 mg/kg (<

30 kg) group. In comparison, levels of sIL-6R were similar and remained high in the other two groups, (i.e., 10 mg/kg (< 30 kg) and 8 mg/kg (\geq 30 kg)).

Levels of C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) decreased upon treatment by Week 1 or Week 2 and then remained low throughout the TCZ treatment period (MRA318JP and WA19977). However, CRP increased prior to each infusion of TCZ and decreased 2 weeks later. This pattern was more evident in the 8 mg/kg (< 30 kg) group than in the other two groups.

2.2.5. What are the key results from the population PK analysis?

See section 2.3.1.

2.2.6. Is the proposed dosing regimen justified?

The dose selection for the registration trial (WA 19977) was based on findings of a clinical study (MRA318JP) conducted in Japanese pediatric patients with PJIA. Tocilizumab given three times with 8 mg/kg every 4 weeks was tested in study MRA318JP. It was observed, that the clinical response in terms of pcJIA50 or pcJIA70, was lower in children with a low bodyweight compared to patients with a higher body weight. The difference in the overall clinical response in patients of different body weights was attributed to difference in systemic exposures of tocilizumab, where patients with lower bodyweight tend to have lower tocilizumab AUC. Alternate dosing regimens were tested by simulation conducted by sponsor. Based on simulation results, a dose of 10 mg/kg in patients weighing < 30 kg would result in similar C_{max} and AUC expected after a dose of 8 mg/kg in patients weighing \geq 30 kg. Although C_{max} and AUC of patients weighing <30 kg following the proposed regimen of 10 mg/kg in the registration trial (WA 19977) was found to be slightly less than patients weighing \geq 30 kg following a dose of 8 mg/kg, the JIA ACR responses at week 16 in Study WA19977 suggest that similar response rates were observed in the two groups.

Refer to the pharmacometric report by Dr. Atul Bhattaram (Appendix I) for additional dose justification details and the review by Dr Nikolay Nikolov, Medical Officer, DPARP, for further information regarding effectiveness/safety of the tested doses.

2.3 Intrinsic Factors

2.3.1. What was the impact of demographic covariates on TCZ exposure?

Sponsor submitted population PK analysis for WA19977 used a two compartment model with parallel first-order and Michaelis-Menton clearance kinetics to characterize the observed PK data. The final population PK model retained the effects of body surface area (BSA) on clearance (CL), height (HT) on central volume of distribution (V₁), BSA on peripheral volume of distribution (V₂), and both BSA and Serum creatinine (SCRT) on the maximum elimination rate (VM). IL-6 and sIL-6R as time-varying covariates were shown to have no impact on the PK profile of TCZ. Dr. Bhattaram's analysis confirmed sponsor's estimates.

The significance of these identified covariates on PK parameters such as CL and V1 is shown in Table 6.

Table 6. Summary of Population PK Parameters from Final Model Developed for WA19977

Statistically Significant Effect	Relationship	Covariate Range [min, max]	% Change in PK Parameters from Typical Value [min, max]
BSA (m ²) on CL	$CL = 0.14 \times (BSA/1.25)^{0.804}$	[0.5, 2]	[-52, +46]
HT (cm) on V1	$V1 = 1.98 \times (HT/143.2)^{2.23}$	[85, 180]	[-69, +67]
BSA (m ²) on V2 and VM	$V2 = 2.1 \times (BSA/1.25)^{0.992}$ $VM = 6.58 \times (BSA/1.25)^{0.992}$	[0.5, 2]	[-60, +59]
SCRT (μmol/L) on VM	$VM = 6.58 \times (SCRT/43)^{-0.239}$	[19, 82]	[+22, -14]

Reviewer's comment: Body size as measured by BSA was found to be the most influential covariate for the linear part of and the overall clearance, central volume of distribution, and peripheral volume of distribution. The proposed dose is based on another measure of body size, the body weight, which should be highly correlated to BSA. Therefore, the body weight based dosing strategy by matching PK exposure for different body weight groups seems reasonable.

2.3.2. What were the immunogenicity findings for TCZ? What was the impact of immunogenicity on exposure, efficacy, and/or safety?

One patient in study WA19977 developed anti-drug antibodies following 10 mg/kg TCZ treatment in Part I of the study. Her associated PK concentrations from baseline through week 12 post dose were comparable to those from other patients and did not experience infusion reactions. The patient was withdrawn due to lack of efficacy response based on JIA ACR30 at the end of Part I and was therefore discontinued from Part II.

One patient in studies MRA318JP/319JP developed neutralizing antibodies before the fourth infusion and was tested positive for IgE antibodies after the fifth infusion (657 days after the fourth infusion). In the latter case, the patient did not experience any AEs associated with this infusion, but was withdrawn from the study as per protocol-specified withdrawal criteria.

Reviewer's comment: The impact of immunogenicity on PK exposure, efficacy, and/or safety remains inconclusive for pJIA population given its low incidence and small database.

3 Labeling Recommendation

Below is the text added to the approved label for Clinical Pharmacology relevant information. Labeling statements to be removed are shown in ~~striketrough font~~ and suggested labeling to be included is shown in underline font.

Polyarticular Juvenile Idiopathic Arthritis

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

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

APPENDIX I
OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 What is the rationale behind the proposed tocilizumab dose/dosing regimen in patients with polyarticular juvenile idiopathic arthritis(PJIA)?

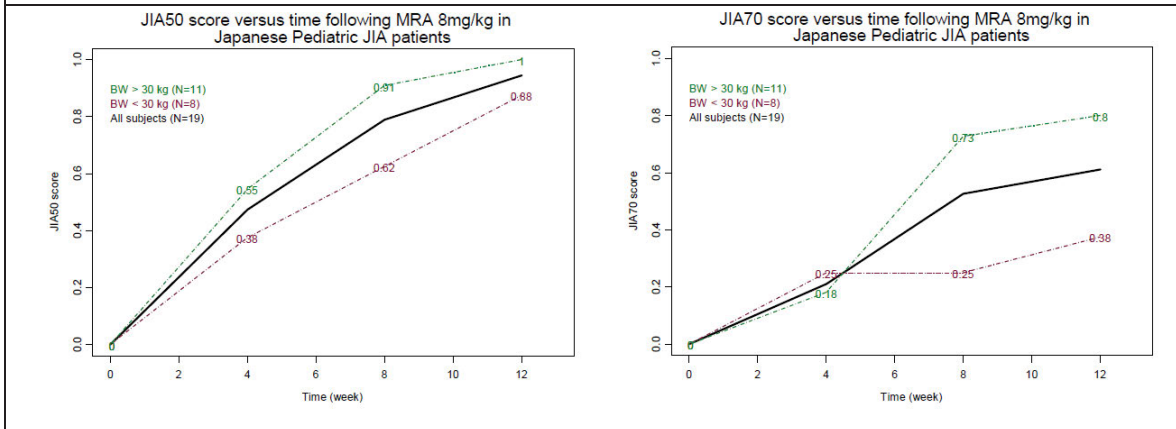
Table 1 shows the proposed dosing regimen in patients with PJIA.

Polyarticular Juvenile Idiopathic Arthritis (2.2)	
Recommended 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

Source: Proposed drug label

The dose selection for the registration trial (WA 19977) was based on a clinical study (MRA318JP) conducted in Japanese pediatric patients with PJIA. The objectives of study MRA318JP was to determine the efficacy, safety and pharmacokinetics of tocilizumab when dosed three times with 8 mg/kg every 4 weeks. It was observed, that the clinical response, expressed as probability to reach a pcJIA50 or pcJIA70 score, was lower in children with a low bodyweight compared to patients with a higher body weight. After 12 weeks of treatment with tocilizumab 8 mg/kg every 4 weeks, 88% of the patients reached a pcJIA50 score and 38% reached pcJIA70 for body weight < 30 kg, whilst 100% reached pcJIA50 and 80% reached pcJIA70 in the group with a body weight ≥ 30 kg (Figure 1).

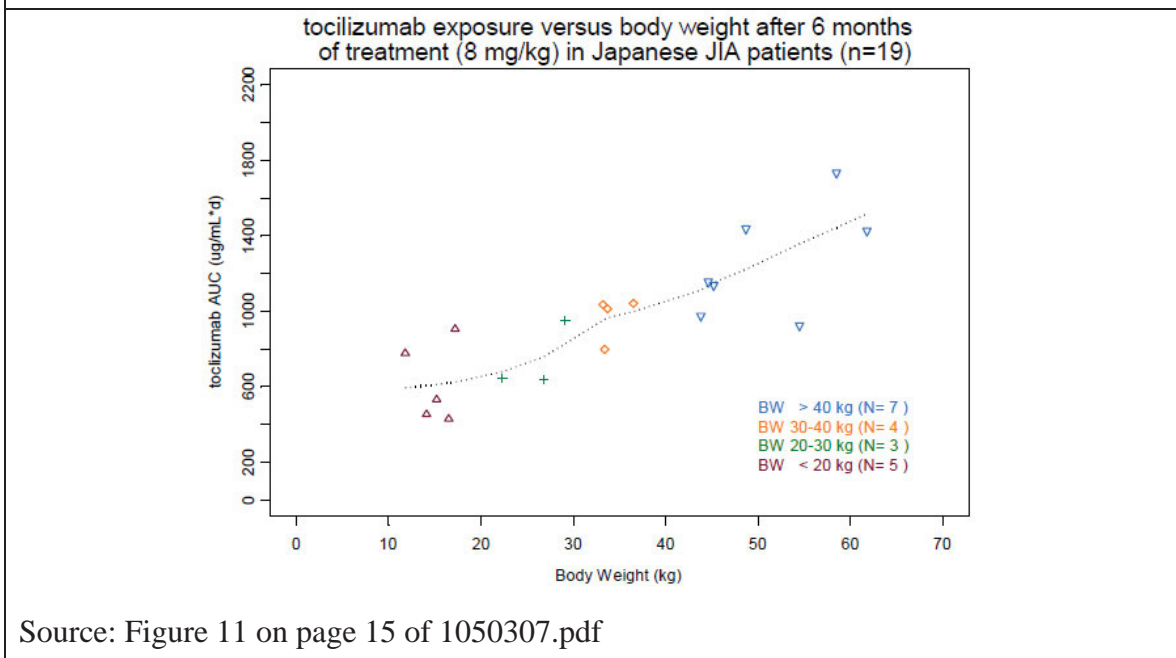
Figure 1. Time course of pcJIA50 score (left panel) and pcJIA70 score (right panel) in Japanese pediatric pcJIA patients (MRA318JP); 8 mg/kg every 4 weeks in two body weight categories (numbers on dotted lines indicate the probability to reach pcJIA50 or pcJIA70 score)



Source: Figure 1 on page 2 of 1050307.pdf

The differences in the clinical response (JIA50, JIA70) between patients less than 30 kg and greater than 30 kg was attributed to differences in systemic concentrations of tocilizumab. Figure 2 shows calculated (based on population pharmacokinetic model) tocilizumab AUC versus bodyweight after 6 months of treatment (8 mg/kg). The findings suggested that patients with lower bodyweight had lower tocilizumab AUC.

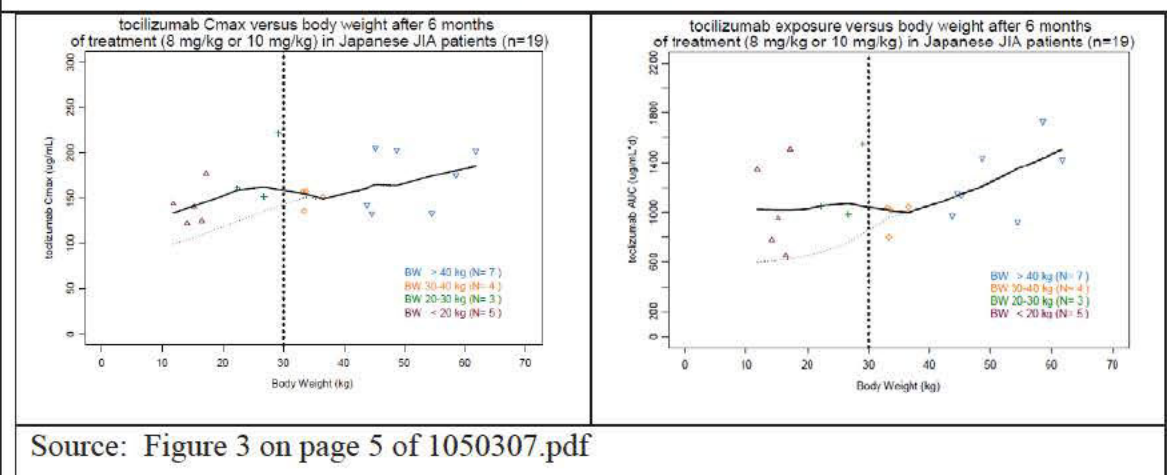
Figure 2. Tocilizumab AUC versus body weight after 6 months of treatment (8 mg/kg) in Japanese JIA patients (n=19)



Source: Figure 11 on page 15 of 1050307.pdf

Sponsor conducted simulations using alternate dosing regimens to achieve similar tocilizumab concentrations across weight groups. The results of simulations suggested that a dose of 10 mg/kg in patients weighing less than 30 kg would result in similar C_{max} and AUC expected after a dose of 8 mg/kg in patients weighing greater than or equal to 30 kg (Figure 3).

Figure 3. Tocilizumab C_{max}(left), AUC(right) versus body weight after 6 months of treatment (8 mg/kg or 10 mg/kg) in Japanese JIA patients



Source: Figure 3 on page 5 of 1050307.pdf

Figure 4 shows the time course of tocilizumab concentrations in the registration trial (WA 19977) confirming the dose selection strategy. Table 2 shows the JIA ACR response at week 16 in Study WA19977. The data suggests that similar response rates were observed in the two groups (10 mg/kg in patients with body weight less than 30 kg versus 8 mg/kg in patients with body weight greater than or equal to 30 kg).

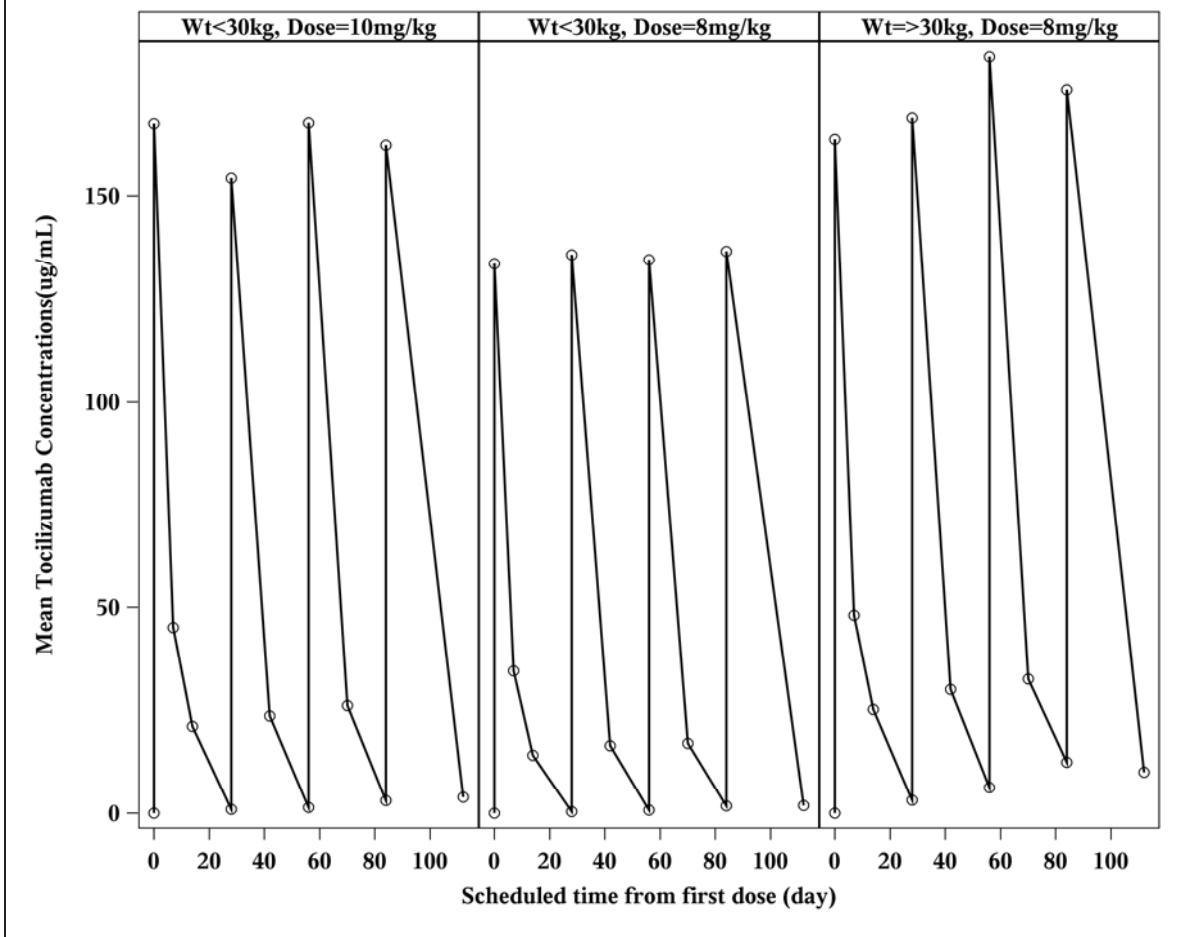
Table 2. JIA ACR Response Rates During the Open-Label Lead-in Period, Week 0-16 (Part I), Study WA19977

JIA ACR Response at Week 16, by Dosing Regimen, Study WA19977				
	BW <30 kg		BW ≥30 kg	All TCZ
	TCZ 10 mg/kg	TCZ 8 mg/kg	TCZ 8 mg/kg	
N	35	34	119	188
ACR30, n (%)	31 (89%)	26 (77%)	111 (93%)	168 (89%)
ACR50, n (%)	28 (80%)	24 (71%)	104 (87%)	156 (83%)
ACR70, n (%)	22 (63%)	14 (41%)	81 (68%)	117 (62%)
ACR90, n (%)	11 (31%)	8 (24)	30 (25%)	49 (26%)

Source: CSR WA19977, adapted from Tables 10 and etepfrq01 w16 it1 ap1

For further information on effectiveness/safety of the tested doses please refer to the review by Dr Nikolay Nikolov, Medical Officer, DPARP for further details.

Figure 4. Mean Tocilizumab concentrations in study WA 19977.



1.2 Recommendations

Please see proposed changes to labeling statements.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Polyarticular Juvenile Idiopathic Arthritis

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 [REDACTED] ^{(b) (4)} 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 4 weeks, ~~the estimated~~ [REDACTED] ^{(b) (4)} mean (\pm SD) AUC_{4weeks}, C_{max} and C_{min} of

tocilizumab were 29500 ± 8660 mcg·hr/mL, 182 ± 37 mcg/mL and 7.49 ± 8.2 mcg/mL, respectively.

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

2 PERTINENT REGULATORY BACKGROUND

Tocilizumab (Actemra®, RO4877533, TCZ) is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against the soluble and membrane-bound interleukin 6 receptor (sIL-6R and mIL-6R).

The current pediatric program was conducted to fulfill the requirements for TCZ outlined in the Pediatric Research Equity Act (PREA) for the initial indication of adult RA, and to support this sBLA filing for the following indication:

Actemra is indicated for the treatment of active pJIA in patients 2 years of age and older.

To investigate the pharmacokinetic characteristics and the exposure-efficacy and safety relationships of tocilizumab in the pJIA population, available data from study WA19977 were analyzed using a population approach. This study was a 24-week randomized double-blind, placebo controlled withdrawal trial with a 16-week open label lead-in-phase, and 64-week open label follow-up, to evaluate the efficacy and safety of tocilizumab in patients with active polyarticular-course juvenile idiopathic arthritis.

The sponsor's report describes the investigation and analyses results of the population pharmacokinetic analysis and graphical exposure-efficacy and safety analyses of tocilizumab in pediatric patients with pJIA. In this review, the reviewer mainly focused on population pharmacokinetic analysis. The proposed labeling statements are derived based on population pharmacokinetic analysis.

3 RESULTS OF SPONSOR'S ANALYSIS

The final PK dataset consist of 2631 tocilizumab serum concentrations collected from 188 pJIA patients. The number of serum concentrations per treatment group per treatment time period is provided in Table 3 below.

Table 3. Number of serum concentrations per treatment group per treatment time period.

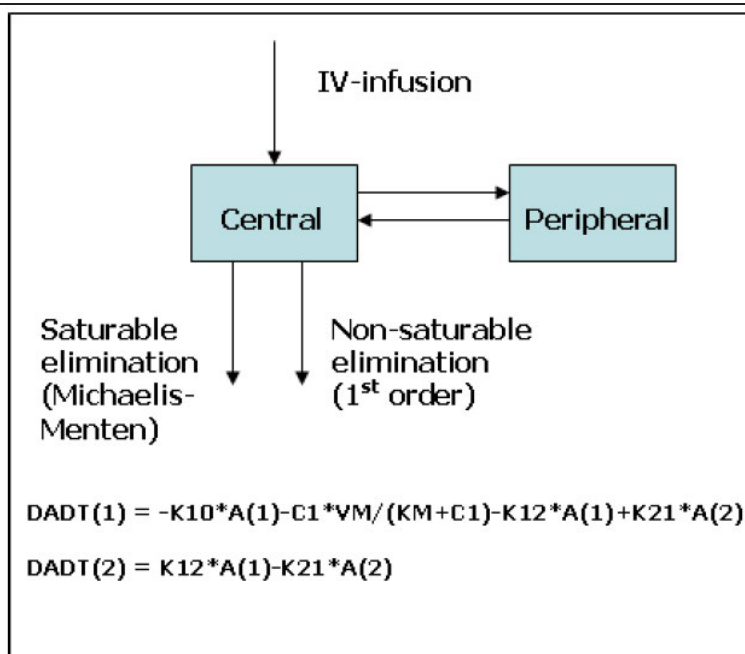
Treatment Group	No. serum concentration / No. patients			
	Total	Part I	Part II	Part III
8 mg/kg (< 30 kg)	367 / 34	296 / 34	61 / 16	10 / 8
10 mg/kg (< 30 kg)	468 / 35	339 / 35	110 / 22	19 / 15
8 mg/kg (≥ 30 kg)	1796 / 119	1254 / 119	450 / 83	92 / 67
Total	2631 / 188	1889 / 188	621 / 121	121 / 90

Source: Table 4 on Page 24 of wa19977-pk.pdf report

The population PK model developed for the adult RA patients and the sJIA patients were used as a base model (Figure 5). This was a two-compartment model including both a saturable and non-saturable elimination pathway to describe the nonlinearity in the pharmacokinetics. The compartmental models were parameterized in terms of clearances and volumes of distribution.

Runs with both, log-transformed data and untransformed data were tested. First Order Conditional Estimation (FOCE) with interaction was used as it is the preferred method in case of rich data per subject, highly non-linear model or considerable between-patient variability.

Figure 5. Pediatric structural pharmacokinetic model for TCZ with combined 1st-order and Michaelis-Menten elimination.



Source: Figure 2 on page 4 of 1050307.pdf

Table 4 shows the demographic data included in the pharmacokinetic analysis.

Table 4. Summary of demographic data (continuous covariates).

Covariate	Total (n=188)	8 mg/kg (< 30 kg, n=34)	10 mg/kg (< 30 kg, n=35)	8 mg/kg (≥ 30 kg, n=119)
	Mean (Std) Median (Min/Max)	Mean (Std) Median (Min/Max)	Mean (Std) Median (Min/Max)	Mean (Std) Median (Min/Max)
Age (year)	11 (4) 11 (2/17)	7.6 (2.7) 7.5 (3/15)	6.9 (3) 7 (2/12)	13.1 (2.8) 13 (6/17)
Body Weight (kg)	39.6 (17.3) 39.2 (9.6/85.1)	22.4 (5.3) 22.5 (10.8/29.6)	20.7 (5.7) 20.9 (9.6/29.5)	50 (12.6) 48.4 (30.7/85.1)
Height (cm)	140.8 (21.9) 143.2 (85/180)	120.4 (14.1) 122 (92.2/146.8)	117.1 (15.3) 121 (85/145)	153.5 (13.7) 154.2 (109/180)
Body Mass Index (kg/m ²)	18.9 (4.5) 18.3 (11.9/35.4)	15.2 (1.6) 15.1 (11.9/18.8)	14.8 (1.6) 14.5 (12.2/18.4)	21.1 (4.2) 20.3 (14.7/35.4)
Body Surface Area (m ²)	1.2 (0.4) 1.25 (0.5/2)	0.9 (0.2) 0.9 (0.5/1.1)	0.8 (0.2) 0.9 (0.5/1.1)	1.5 (0.2) 1.4 (1/2)

Source: Table 5 on Page 25 of wa19977-pk.pdf report

Figure 6 shows observed data and lines based on pharmacokinetic model. The model described the data reasonably well.

Figure 6. Full profile and selected visits for individual serum concentration time course (linear Y-axis). The points represent the observed serum concentrations. The full lines represent the individual predicted serum concentration time course. The dotted lines represent the population predicted serum concentration time course.

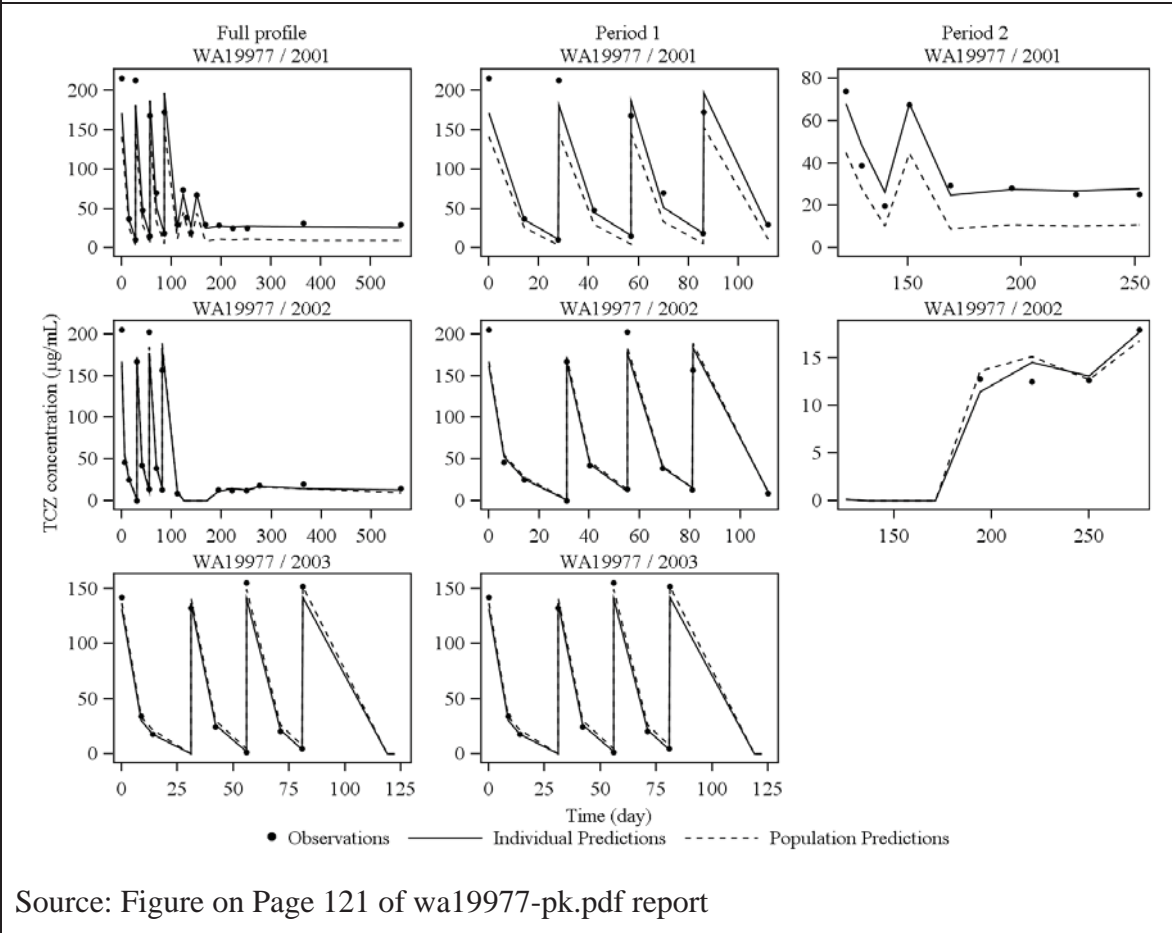


Table 5 shows the estimates of the pharmacokinetic parameters.

Table 5. NONMEM parameter estimates for the final PK model.

Parameter	Unit	Estimate	RSE (%)
Fixed Effects			
CL	L/day (mL/hr)	0.14 (5.83)	4.91
V1	L	1.98	1.28
Q	L/day (mL/hr)	0.521 (21.7)	7.33
V2	L	2.1	3.66
VM	mg/day (mg/hr)	6.58 (0.274)	5.2
KM	µg/mL	0.765	22.2
Random Effects BPV*			
CL	CV%	29.2	23.1
V1	CV%	12.7	17.7
V2	CV%	29.3	18.0
VM	CV%	31.6	19.0
Correlation CL-V1	-	-0.29	-
Correlation CL-V2	-	-0.79	-
Correlation CL-VM	-	-0.72	-
Correlation V1-V2	-	0.81	-
Correlation V1-VM	-	0.73	-
Correlation V2-VM	-	0.91	-
Covariate Effects			
Effect of BSA on CL	-	0.804	13.3
Effect of HT on V1	-	2.23	3.14
Effect of BSA on V2 & VM	-	0.992	8.91
Effect of SCRT on VM	-	-0.239	23.5
Error Model			
σ_1 (additive)	µg/mL	1.14	2.75
σ_2 (proportional)	%	16.3	1.3

RUNID: RUN030, OFV: 11941.525

BPV – Between-patient variability, σ – Residual error, RSE – Relative standard error of estimate, OFV – Objective function value, * – RSE was obtained only for the variances

Source: Table 13 on Page 33 of wa19977-pk.pdf report

Proposed labeling statements

The sponsor proposed labeling statements are based on the estimated pharmacokinetic parameters (Table 5). For providing information on C_{max}, C_{min} and accumulation ratios, sponsor derived them using the model and estimated pharmacokinetic parameters (Table 6). The labeling statements are discussed in Section 1.3 (Labeling Statements).

Table 6. Summary of TCZ Pharmacokinetic Exposure Parameters to Week 16 by Treatment Group (Part I)

PK Parameters	TCZ 10 mg/kg (< 30 kg)	TCZ 8 mg/kg (< 30 kg)	TCZ 8 mg/kg (≥ 30 kg)
Model Computed	n = 32	n = 30	n = 115
AUC _{wk12-16} , µg·day/mL	968±254 (934, 445-1658)	702±218 (712, 336-1239)	1231±361 (1157, 610-2228)
C _{max_wk12} , µg/mL	175±32 (175,108-256)	140±25 (141, 92-187)	182±37 (179,107-341)
C _{min_wk16} , µg/mL	2.35±3.59 (0.88, 0-16.3)	0.95±2.07 (0.09, 0.0-7.7)	7.49±8.20 (4.11, 0.0-36.3)
Observed	n = 29	n = 27	n = 113
C _{wk16}	2.75±4.19 (1.02, 0.0-18.7)	0.98±2.26 (0.0, 0.0-9.06)	7.44±8.48 (4.4, 0.0-39.1)

Source: [std1_pk_1](#)

Mean ± SD (median, min-max) was presented; n: represents number of patients contributing to summary statistics; C_{wk16}: observed pre-dose concentration at Week 16; AUC_{wk12-16}, C_{max_wk12} and C_{min_wk16} are pharmacokinetic model computed. The sample size for the observed C_{wk16} is smaller when compared to that of the model-computed PK parameters because of the missing samples at Week 16.

Source: Table 3 on Page 18 of summary-clin-pharm.pdf

Reviewer's Comments: The reviewer was able to run the final population pharmacokinetic model and confirm sponsor's estimates as reported in Table 5. Table below shows the summary of TCZ pharmacokinetic exposure parameters to week 16 as calculated by reviewer and are similar to those reported by sponsor in Table 6.

Parameter	WT<30kg 10mg/kg	WT<30kg 8mg/kg	WT≥30kg 8mg/kg
AUC _{wk12-16} (ug.day/mL)	959.7371	688.1643	1203.824
C _{max_wk12} (ug/mL)	174.0666	139.0497	178.9482
C _{min_wk16} (ug/mL)	2.412261	1.321169	8.266617

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR
WA19977-pk.pdf	Population Pharmacokinetic Analysis and Exposure-Efficacy and Safety Analyses of Tocilizumab for Study WA19977 in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis	

4 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
SASCodeforNONMEM dataset	SAS code for creating NONMEM dataset	
Run030.ctf	Population pharmacokinetic model (Final)	
Run030 fit	Output of final population pharmacokinetic model	
Run020.lst	Parameter estimates from final population pharmacokinetic model	

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

/s/

LIANG ZHAO
03/22/2013

VENKATESH A BHATTARAM
03/24/2013

SURESH DODDAPANENI
03/25/2013

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125276	Brand Name	ACTEMRA
OCP Division (I, II, III, IV, V)	II	Generic Name	Tocilizumab
Medical Division	DPARP	Drug Class	Anti-human IL-6 receptor mAb
OCP Reviewer	Elizabeth Shang, Ph.D.	Indication(s)	
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Injectable
Pharmacometrics Reviewer	Venkatesh Bhattaram, Ph.D.	Dosing Regimen	8 mg every two weeks in patients \geq 30kg; 10 mg every two weeks in patients < 30 kg
Date of Submission	6/28/2012	Route of Administration	IV
Estimated Due Date of OCP Review		Sponsor	Roche
Medical Division Due Date		Priority Classification	S
PDUFA Due Date	April 29, 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	X	3	3	
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	3	3	
Population Analyses -				
Data rich:				
Data sparse:	X	3	3	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3	3	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate	X			

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			This study fulfills PREA requirement
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

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

Elizabeth Shang, Ph.D.

August 21, 2012

Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni, Ph.D.

Team Leader/Supervisor

Date

BACKGROUND

In US, tocilizumab (TCZ) is currently approved for adult rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (SJIA) in patients 2 years and older. The original approval for RA was based upon 24-week efficacy and safety data from five pivotal Phase 3 studies. The dose regimen for RA is 4 mg per kg IV followed by an increase to 8 mg per kg based on clinical response in combination with DMARDs or as monotherapy. The approval for SJIA was based upon a three-part 5-year Phase 3 study (WA18221). Specifically, the application includes: 1) WA18221-Part 1: 12-week efficacy and safety study of TCZ (12 mg/kg dose for patients with body weight < 30 kg and 8 mg/kg dose for patients with body weight \geq 30 kg) in sJIA patients (n=112); 2) Cut of WA18221 data (cut-off date: 10th May 2010) when 50 patients reach one year in Part II of WA18221; 3) additional supportive safety and efficacy data from Japanese sJIA trials containing data for at least 56 patients through to one year. The dose regimen for SJIA is 8 mg/kg IV every two weeks (q2w) for patients with body weight \geq 30 kg, 12 mg/kg IV q2w for patients with body weight < 30kg.

TCZ is approved for the treatment of multi-centric Castleman's Disease, adult RA, SJIA, and polyarticular juvenile idiopathic arthritis (PJIA) in Japan. TCZ has been also approved for the treatment of moderately to severely active RA patients in the European Union (27 countries) and 15 other countries worldwide.

In this supplemental BLA, the sponsor is seeking new indication, treatment of active PJIA in patients 2 years of age and older. In US, the approved drug treatment for PJIA is etanercept, abatacept, and adalimumab.

CLINICAL PHARMACOLOGY PROGRAM

The clinical pharmacology program consists of 1 pivotal Phase 3 study (WA19977), 1 supportive Phase 3 study (MRA318JP), and 1 Phase 4 long-term surveillance study (MRA319JP) (See table below). Study WA19977 is being conducted under a special protocol assessment (SPA) agreement granted on June 8, 2009. This study is also designed to fulfill the PREA requirement to conduct study for PJIA in children 2 to 17 years (inclusive) under original BLA for RA. The Agency waived PREA requirement for patients age younger than 2 years.

Study	Design	Patients
Pivotal phase III trial to evaluate efficacy and safety of TCZ in patients with pJIA:		
WA19977	Two-year study in three parts: <u>Part I</u> : 16-week open-label TCZ therapy: BW ≥ 30 kg: 8 mg/kg TCZ IV q4w BW < 30 kg: 8 or 10 mg/kg TCZ IV q4w <u>Part II</u> : 24-week double-blind, placebo-controlled, randomized withdrawal period in patients achieving JIA ACR30 response at week 16 of Part I; same TCZ dose as in Part I or placebo <u>Part III</u> : 64-week open-label extension (ongoing)	Patients with pJIA for at least six months and with at least five active joints; age at screening was 2-17 years. Treated in <u>Part I</u> : N = 188 (8 mg/kg TCZ: n = 153; 10 mg/kg TCZ: n = 35) Treated in <u>Part II</u> : N = 163 (8 mg/kg TCZ: n = 66; 10 mg/kg TCZ: n = 16; placebo: n = 81)
Supportive trials:		
MRA318JP	12-week open-label, single-arm study; TCZ dose 8 mg/kg IV q4w	Japanese patients with pJIA with at least five active joints; age at baseline 3-19 years; N = 19
MRA319JP	Long-term extension of MRA318JP; total TCZ 8 mg/kg IV q4w treatment duration 0.35–3.53 years	Patients who completed MRA318JP: N = 19
ML21939 (JPMS)	6-month observational cohort study in Japan	pJIA patients: N = 179

BW: body weight.

All studies in this clinical program were conducted in accordance with the principles of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki and its amendments, and the local laws and regulations of the countries in which the research was conducted.

Source data: Section 2.5 Clinical Overview, Table 3

The clinical pharmacology program included PK and PD data and PK-PD relationships from the following studies: Roche's pivotal study WA19977 and two supportive Chugai studies (MRA318JP and MRA319JP).

PIVOTAL STUDY WA19977

Dose Selection Rationale

In the 12-week trial of MRA318JP, the TCZ exposure was lower in patients with a low body weight with 8 mg/kg q4w dosing for all patients. Modeling and simulation results have shown that comparable exposure could be achieved across the body weight range with a 8 mg/kg dose for patients who have a body weight ≥ 30 kg and a 10 mg/kg dose for patients who have a body weight less than 30 kg. This analysis provided the dosing rationale for the pivotal study WA19977.

Population PK Analysis

A population PK model was developed using data from Study WA19977. The influence of covariates (i.e. age, gender, race, body weight, serum creatinine, and creatinine clearance) on the PK parameters was investigated. The systemic PK exposure parameters computed from the population PK model were: AUC_{wk12-16}, AUC_{wk36-40}, C_{max_wk12}, C_{max_wk36}, C_{min_wk16}, C_{min_wk40}. The observed PK exposure parameters summarized were: C_{wk16}: observed pre-dose TCZ concentration at Week 16, and C_{trough}: within-patient average observed pre-dose TCZ concentration from Week 20 to Week 40.

Following administration of TCZ every 4 weeks, mean TCZ pre-dose concentrations trended upwards slightly over time for all treatment groups. Pre-dose concentrations reached stable condition at Week 12.

When mean TCZ serum concentrations were compared among three treatment groups, the 8 mg/kg (≥ 30 kg) group showed slightly higher concentrations than the 10 mg/kg (< 30 kg) group, whereas the 8 mg/kg (< 30 kg) group showed lower concentrations than the other two treatment groups at all sampling points over time (Figure 1).

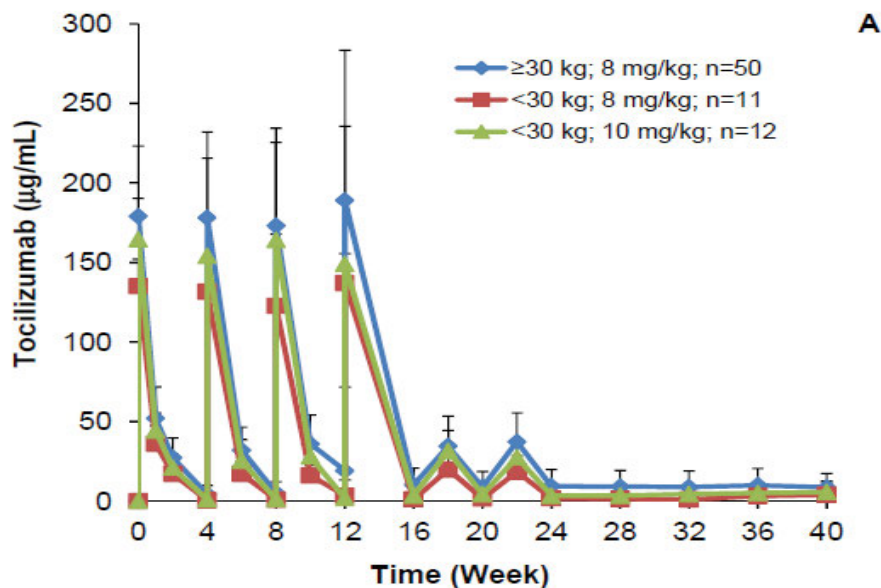
Mean computed PK exposure parameters were slightly lower for the 10 mg/kg (< 30 kg) group compared to the 8 mg/kg (≥ 30 kg) group for AUCwk12-16, Cmin_wk12, and Cwk16, whereas mean values of Cmax_wk12 were similar between the two treatment groups. Reported geometric mean ratios for AUCwk12-16, Cwk16, Cmax_wk12 for 10 mg/kg in < 30 kg group compared to 8 mg/kg in ≥ 30 kg were 0.79, 0.40, and 0.97, respectively.

Computed PK exposures (AUCwk12-16, Cmax_wk12, Cmin_wk16, and Cwk16) for the 8 mg/kg (< 30 kg) group were lower than those from the other two treatment groups. Reported geometric mean ratios for AUCwk12-16, Cwk16, and Cmax_wk12 for the 8 mg/kg (< 30 kg) group compared with the 8 mg/kg (≥ 30 kg) group were 0.57, 0.22, and 0.77, respectively.

By Week 40, mean PK exposure parameters for the 10 mg/kg (< 30 kg) group was slightly lower compared to the 8 mg/kg (≥ 30 kg) group for AUCwk36-40, Cmin_wk40 and Ctrough, but similar for Cmax. The reported geometric mean ratios for AUCwk12-16, Cmax_wk36 and Ctrough, for 10 mg/kg (< 30 kg) group compared to 8 mg/kg (≥ 30 kg) were 0.87, 1.03, and 0.50, respectively.

PK exposures (AUCwk36-40, Cmax_wk36, and Ctrough) for 8 mg/kg (< 30 kg) group were lower than those from the other two treatment groups. Geometric mean ratios for AUCwk36-40, Ctrough, and Cmax_wk36 for the 8 mg/kg (< 30 kg) group compared with the 8 mg/kg (≥ 30 kg) group were 0.62, 0.26, and 0.79, respectively.

Figure 1. Mean Serum TCZ Concentrations by Visit to Week 40.



Source data: Section 2.7.2, Figure 10A

Exposure-Response Analysis

Efficacy end points (JIAACR ACR30/50/70/90 responses) and incidence of adverse events per 100 patient years were summarized by TCZ PK exposure quartiles (AUCwk12-16, Cmax_wk12 and Cwk16 and AUCwk36-40, Cmax_wk36 and Ctrough), respectively.

Patients who did not achieve a JIA ACR30 response at Week 16 were excluded from Part II of the study. The proportion of patients withdrawing at Week 16 for nonsafety reasons (including lack of efficacy) was higher in the 8 mg/kg (< 30 kg) treatment group than the other two groups. As shown, this treatment group had lower exposures and sub-optimal pharmacodynamic responses compared to the other two groups. For this reason, the Part II population is enriched for responders across all treatment groups, and therefore information regarding exposure-efficacy relationship from this part of the study is for patients who achieved a JIA ACR30 response at the end of Part I of the study. Therefore, interpretation of the exposure response relationship should be performed with caution

PD Analysis

Serum concentrations of IL-6, sIL-6R, and C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were summarized graphically and descriptively.

Effect of Weight on PK exposure (was AUCwk12-16, Cmax_wk12, and Cwk16) was assessed. All three PK exposure parameters increased slightly with increase of body weight following 8 mg/kg dosing in patients BW < 30 kg and BW ≥30 kg treatment groups. The reported Pearson correlation coefficient (R) was 0.7289 for AUCwk12-16, 0.5938 for Cmax_wk12 and for 0.5787 for Cmin_wk16, representing low to median association between PK exposure parameters and body weight. Once dose increased to 10 mg/kg in patients BW < 30 kg but kept 8 mg/kg in patients with BW 30 kg, associations between PK exposure parameters and body weight decreased as shown by decreased R for AUCwk12-16 (0.5926), Cmax_wk12 (0.5339) and Cmin_wk16 (0.3474), respectively.

IMMUNOGENICITY

One patient developed positive neutralizing anti-TCZ antibodies at Week 20. This patient (18.4 kg, 3 years old, female) received TCZ 10 mg/kg in Part I of the study.

SUPPORTIVE STUDY MRA318JP

All 19 enrolled Japanese patients contributed PK data to study MRA318JP. There was no appreciable accumulation of TCZ exposure following four infusions at a dose level of 8 mg/kg. The TCZ exposure was lower in patients with a low body weight with 8 mg/kg q4w dosing for all patients. CRP levels and ESR decreased, and sIL-6R concentrations increased following TCZ administration in pJIA patients. The proportion of patients achieving a JIA ACR50 and JIA ACR70 response was lower in children with a low body weight (< 30 kg) compared to patients with a higher body weight (≥ 30 kg).

SUPPORTIVE STUDY MRA319JP

Relationship between serum TCZ concentration and PD markers (CRP, ESR, and sIL-6R) were explored. The percentage of patients achieving JIA ACR30, ACR50, and ACR70 responses were all ~94% at 24 weeks after the start of treatment in the extension. The sponsor reported that there was no clear relationship between the serum TCZ trough concentration and changes in the clinical indices of improvement in joint symptoms. Patients with serum TCZ concentration was maintained at ≥1 µg/mL showed marked improvement in joint symptoms. CRP was negative at all time points at which the serum TCZ concentration was maintained at ≥1 µg/mL.

COMPARISON OF PK/PD DATA BETWEEN PJIA, SJIA, AND ADULT RA PATIENTS

The TCZ exposure parameters AUC, C_{max}, and C_{min} in pJIA patients were compared to those in sJIA patients from phase III study WA18221 and those in adult RA patients from four phase III studies (WA17822, WA17824, WA18062, and WA18063). See table below.

Table 6 Comparison of PK Exposure Parameters in pJIA, sJIA, and Adult RA Patients

Population, Study	Dose Regimen	Mean ± Standard Deviation		
		C _{max} (µg/mL)	C _{min} (µg/mL)	AUC ^a (µg·day/mL)
pJIA, Study WA19977 Part I, n = 177				
	8 mg/kg q4w (BW ≥ 30kg)	182 ± 37	7.49 ± 8.20	1231 ± 361
	10 mg/kg q4w (BW < 30kg)	175 ± 32	2.35 ± 3.59	968 ± 254
	8 mg/kg q4w (BW < 30 kg)	140 ± 25	0.95 ± 2.37	702 ± 218
pJIA, Study MRA318JP, n = 19				
	8 mg/kg q4w	145 ± 34.7	4.88 ± 4.68 ^b	1054 ± 280 ^c
sJIA, Study WA18221, n = 75				
	8 mg/kg q2w (BW ≥ 30kg)	226 ± 54.5	54.5 ± 20.7	1337 ± 409 ^b
	12 mg/kg q2w (BW < 30kg)	263 ± 54.1	60.5 ± 25.5	1346 ± 426 ^b
Adult RA, Studies WA17822, WA17824, WA18062, WA18063, n = 1820				
	8 mg/kg q4w	187 ± 85	8.6 ± 8.9	1417 ± 613
	4 mg/kg q4w	88 ± 41	1.4 ± 1.9	538 ± 239

All PK parameters were PK model-computed, except for MRA318JP where non-compartmental analysis was used.

BW: body weight.

^a AUC over dosing interval, ie, AUC_{2 weeks} for sJIA (q2w dosing) and AUC_{4 weeks} for pJIA and adult RA (q4w dosing).

^b week 12.

^c AUC_{inf} for first dose.

Source Data: Section 2.5 Clinical Overview, Table 6.

ANALYTICAL METHODS

Determination of the concentration of TCZ in human serum samples from Study WA19777 were conducted using established and previous validated immunoassay procedures (ELISA). The limit of quantification is 0.1 µg/mL for TCZ.

CONCLUSIONS

It is fileable from clinical pharmacology perspective.

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/s/

ELIZABETH Y SHANG
08/22/2012

SURESH DODDAPANENI
08/22/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

**SECOND ADDENDUM TO THE
PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)
MODIFICATION FOR ACTEMRA**

Date: May 1, 2013

Reviewer: Carolyn L. Yancey, M. D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)

Anahita Tavakoli, M. A., Health Communication Analyst, DRISK

Team Leader: Kendra Worthy, Pharm. D., DRISK

Division Director: Claudia Manzo, Pharm.D., Director, DRISK

Drug Name: ACTEMRA (tocilizumab) Injection for Intravenous Infusion

Therapeutic Class: Human Interleukin-6 Receptor (IL-6) Antagonist

Dosage and Route: *Adult dosage: every 4 weeks, 4 mg/kg followed by 8 mg/kg based on clinical response*
Pediatric dosage in Systemic Juvenile Idiopathic Arthritis (S-JIA) every 2 weeks, 12 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg

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

Application Type/Number: BLA 125-276/Supplement 64.4/Sequence 119 received on October 24, 2012

PDUFA Date: April 29, 2013

Applicant: Genentech, Inc. (Genentech), A Member of the Roche Group

OSE RCM #: 2013-87

This brief *second* Addendum is to document insertion of the revised indication statement in labeling, replacing “TNF antagonist therapies” with “Disease-Modifying Anti-Rheumatic Drugs (DMARDs)”¹ in the appropriate appended REMS materials (*Dear Healthcare Provider letter* and the *journal information pieces*). See the **Attachment** of the clean version the REMS Document and revised appended materials.

Attachment

Initial REMS Approved: 01/08/2010

Most Recent Modification: MM/DD/YYYY

BLA 125276 ACTEMRA[®] (tocilizumab)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080

I. GOALS

The goal of the ACTEMRA REMS is:

- To inform healthcare providers about the serious risks associated with ACTEMRA.

II. REMS ELEMENTS

A. Communication Plan (FDCA Section 505-1(e)(3))

In accordance with FDCA 505-1(e)(3), Genentech, A Member of the Roche Group, will implement a communication plan to the following adult and pediatric healthcare providers:

- Rheumatologists and rheumatology healthcare providers who are likely to prescribe ACTEMRA
- Infectious disease specialists who may be consulted about serious infection

¹ In response to revisions to the Actemra labeling (approved on October 11, 2012), the applicant submitted an amendment to the proposed REMS modification (received on October 24, 2012) with revised text in the indication statement.

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/s/

CAROLYN L YANCEY

05/01/2013

2nd Addendum responds to revised indication statement in revised labeling (approved on October 11, 2012)

CLAUDIA B MANZO

05/01/2013

concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

ADDENDUM TO THE
PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)
MODIFICATION FOR ACTEMRA

Date: April 25, 2013

Reviewer: Carolyn L. Yancey, M. D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)
Anahita Tavakoli, M. A., Health Communication Analyst, DRISK

Team Leader: Kendra Worthy, Pharm. D., DRISK

Division Director: Claudia Manzo, Pharm.D., Director, DRISK

Drug Name: ACTEMRA (tocilizumab) Injection for Intravenous Infusion

Therapeutic Class: Human Interleukin-6 Receptor (IL-6) Antagonist

Dosage and Route: *Adult dosage:* every 4 weeks, 4 mg/kg followed by 8 mg/kg based on clinical response
Pediatric dosage in Systemic Juvenile Idiopathic Arthritis (S-JIA) every 2 weeks, 12 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg

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

Application Type/Number: BLA 125-276/Supplement 64/Sequence 134 received on April 23, 2013

PDUFA Date: April 29, 2013

Applicant: Genentech, Inc. (Genentech), A Member of the Roche Group

OSE RCM #: 2013-87

This Addendum is to document the Division of Risk Management (DRISK) review of the applicant's response to the Agency's Risk Evaluation and Mitigation Strategy (REMS) Assessment Information Request (IR) sent on April 22, 2013. The IR required the applicant to respond to the following:

1. Explain how the approved Actemra REMS is currently functioning
2. Discuss whether or not there is a change to the benefit-risk observed in the clinical trials for the new proposed indication for treatment of active polyarticular juvenile idiopathic arthritis (P-JIA) in patients 2 years of age and older that would necessitate additional modification to the REMS
3. Clarify the rationale for additional information added to the appended REMS materials in the proposed Actemra REMS modification (submitted in Supplement 064/Sequence 097 received on June 28, 2012).

The applicant's response (received on April 23, 2013/Sequence 134) to the Agency's IR contains acceptable clarification and explanation in regard to how the current REMS is functioning, conclusions based on the 18-month and 3-year REMS assessment reports (received on Jul7, 2011 and January 3, 2013, respectively), and the rationale for the proposed REMS modification with revised appended REMS materials (Sequence 097). See the **Discussion and Conclusion Section**, in this Addendum, for details of the applicant's response.

Background

Under the Food and Drug Administration Safety and Innovation Act (FDASIA), an efficacy supplement submitted to a new drug application (NDA) or biologic license application (BLA) with an approved REMS must have an accompanying REMS assessment. The efficacy supplement (064) with a proposed Actemra REMS modification did not include an accompanying REMS assessment or rationale of whether or not the benefit risk of Actemra has changed based on the clinical trials in a different population (patients 2 years of age and older) with a different disease (active P-JIA) and the impact of such a change on the approved REMS and appended REMS materials.

The original REMS for Actemra was approved on January 8, 2010 with the most recent REMS modification approved on October 11, 2012. The REMS consists of a communication plan and a timetable for submission of assessments. See previous DRISK reviews (footnoted in the attached review written on April 9, 2013) for the background and regulatory history of the original Actemra REMS and REMS Modifications.

Regulatory History

The regulatory history specific to this submission under sBLA 125276/Supplement 064/Sequence 134 follows:

- March 5, 2013: The Agency sent fax notification to the applicant that the 90-day discussion period for the Actemra REMS assessment is being opened and provided comments on the applicant's proposed additional appended (b) (4) (b) (4). The Agency recommended that the applicant modify the *Prescriber Education Slide Deck* rather than add (b) (4) (u) (4).

- April 2, 2013: (Supplement 82/Sequence 130) The applicant submitted a proposed REMS modification with revision to the REMS Document and to the *Prescriber Education Slide Deck* in response to *comments* from the Agency in regard to DRISK review of the 3-year REMS assessment. This submission is being reviewed separately from the proposed REMS modification submitted with efficacy supplement 064/Sequence 097.
- April 22, 2013: The Agency sent the applicant a REMS Assessment IR letter via fax to request a targeted REMS assessment of the current REMS for Actemra, clarification of whether or not there is a change in the benefit risk of Actemra in clinical trials for the new proposed indication in P-JIA and the new population that would necessitate additional modification to the REMS elements and/or appended REMS materials.
- April 23, 2013: (Supplement 064/Sequence 134) The applicant submitted a response to the Agency's IR letter sent on April 22, 2013.

Materials Reviewed

The following materials, listed by document date, are reviewed from sBLA 125-276 (Supplement 064) in regard to the proposed Actemra REMS modification based on the proposed new indication in P-JIA:

- April 23, 2013: (Sequence 134) Response to the Agency's IR letter with explanation of how the current REMS is functioning, conclusions about REMS assessments, and the rationale for the additional information proposed to the REMS Document, the appended REMS materials (*Dear Healthcare Provider letter, journal information pieces, Prescriber Education Slide Deck, and the REMS website*)

Review of the Current Actemra REMS Assessment under the New Proposed Indication for Polyarticular JIA in Efficacy Supplement 064

The applicant's responses (received on April 23, 2013/Supplement 064/Sequence 134) to the Agency's IR request (based on the proposed REMS modification for the proposed new indication in P-JIA) are as follows:

Risks with Actemra and the New Proposed Indication for Treatment of P-JIA

The applicant concludes that identified risks with use of tocilizumab in the P-JIA patient population are consistent with those seen in adult rheumatoid arthritis (RA) and can be managed via the current approved Actemra REMS. The applicant states that, "no data have been seen in this population that would warrant additional REMS elements to manage the risks."

Current REMS Components

The Actemra REMS includes the goal to inform healthcare providers about the serious risks associated with Actemra. The REMS elements consist of a communication plan and a timetable for submission of assessments. See the **Attachments** to the DRISK review (written on April 9, 2013) with a minor edit (to update the most recent modification date) in the header of the REMS Document and insertion of the new proposed indication in P-JIA to specific appended REMS materials.

18-Month and 3-Year REMS Assessments

The applicant acknowledges that the 18-month and 3-year REMS assessment reports demonstrate high prescriber knowledge about prescribing of Actemra, serious adverse events associated with use of Actemra, and patient counseling. However, both REMS assessment reports show that knowledge levels were lower for prescriber survey questions about understanding the risk of demyelination, recommended laboratory monitoring, and actions that a prescriber should take, for example, discontinuing Actemra REMS when certain patient laboratory results are observed. The Agency required a REMS modification based on the 18-month REMS assessment review with addition of a Prescriber Education Slide Deck to improve prescriber awareness of the above three risks. The REMS Modification was approved on June 20, 2012).

The applicant concludes, “satisfaction with the results of the 3-year REMS assessment considering the complexity of the laboratory monitoring survey questions...” However, the applicant recognizes that the REMS is not fully meeting its goals based on FDA’s evaluation of the 18-month assessment.

Proposed REMS Modification (Sequence 123) in Response to the 3-year REMS Assessment Comments

- The applicant’s proposed REMS modification (based on the 3-year REMS assessment) includes (b) (4) (b) (4) with use of Actemra. In response to this proposed (b) (4), the Agency recommended (Comments sent to the applicant on March 5, 2013) that rather than adding (b) (4), that the applicant revise the Prescriber Education Slide Deck to clarify recommended actions for prescribers to take based on laboratory abnormalities to better support prescriber understanding of the laboratory parameters and possible clinical consequences.
- The Agency required that an additional REMS assessment be completed by the applicant at 5 years post approval (January 8, 2015). The applicant proposed that the (b) (4) (b) (4)

REMS Modification Based on the Proposed New Indication for Treatment of P-JIA (Efficacy Supplement 064/Sequence 097 received June 28, 2013)

See DRISK Review of the Proposed REMS Modification (written on April 9, 2013) that is attached to this **Addendum**.

As stated by the applicant, “Once this REMS modification is approved, the following actions will be conducted:

- The Dear Healthcare Provider letter will be distributed within 60 days to adult and pediatric prescribers to include the same target prescribers as listed in the approved REMS, communication plan.
- The Prescriber Education Slide Deck will be updated with the appropriate materials and revised Prescribing Information. The REMS website will be updated to include links to revised appended materials.

- The Prescriber Education Slide Deck will be presented to appropriate prescribers. The information piece in the Journal of oncology will be printed for 5 years following product approval.
- The timetable for submission of assessments will include a 5-year REMS assessment from the applicant.

Impact of a REMS modification on any future REMS assessment

As acknowledged by the applicant, if the proposed new indication in P-JIA is approved by the Agency, the REMS modification based on this new indication "... will impact any future REMS assessments in that the survey questionnaire will also be provided to healthcare prescribers who prescribe Actemra for the P-JIA indication.

Discussion and Conclusion

There are no new safety risks observed in the clinical trials for the new proposed indication in P-JIA indication and patient population. The applicant's response to the Agency's IR on the current REMS assessment (received on April 23, 2013) is acceptable to the DRISK and the DPARP.

Recommendations

The DRISK recommends acceptance of the applicant's response (received on April 23, 2013) to the Agency's request for a required REMS assessment under efficacy supplement 064, proposed for the new indication in P-JIA (received on June 28, 2012).

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/s/

CAROLYN L YANCEY

04/25/2013

Addendum to Review a Current REMS Assessment under Efficacy Supplement 064 for new indication in P-JIA

CLAUDIA B MANZO

04/25/2013

concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**Proposed Modification to the ACTEMRA Risk Evaluation and Mitigation Strategy
(REMS) for the Proposed Indication in the Treatment of
Polyarticular Juvenile Idiopathic Arthritis**

Date: April 1, 2013; *Revised April 9, 2013*

Reviewer(s): Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)
Anahita Tavakoli, M.A., Health Communications Analyst, DRISK

Team Leader: Kendra Worthy, Pharm.D., DRISK

Division Director: Claudia Karwoski, Pharm.D., DRISK

Drug Name: ACTEMRA (tocilizumab) Injection for Intravenous Infusion

Therapeutic Class: Human Interleukin-6 Receptor Inhibitor

Dosage and Route: *Adult dosage: every 4 weeks, 4 mg/kg followed by 8 mg/kg based on clinical response.*
Pediatric dosage in Systemic Juvenile Idiopathic Arthritis (S-JIA): every 2 weeks - 12 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg

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

Application Type/Number: BLA 125-276 (Supplement 064/Sequence 097) received on June 28, 2012

PDUFA Date: April 29, 2013; *Revised Goal Date April 22, 2013*

Sponsor: Genentech, Inc

OSE RCM #: 2012-1861

TSI #: Closed #1086 (Infections, GI Perforations, Liver function Change) on November 14, 2012

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1 INTRODUCTION

This is a review of Genentech's proposed modification to the Actemra Risk Evaluation and Mitigation Strategy (REMS) received on June 28, 2012 (Efficacy Supplement 064/Sequence 097) to incorporate the proposed new indication in the treatment of polyarticular juvenile idiopathic arthritis (P-JIA) in patients 2 years and older. This Supplement is submitted to the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP). The potential serious safety risks associated with use of Actemra that require a REMS are unchanged in this efficacy supplement for P-JIA.¹

The original REMS for Actemra was approved on January 8, 2010 with the most recent REMS modification approved on October 11, 2012. The REMS consists of a communication plan and a timetable for submission of assessments.

The applicant's proposed modification to the Actemra REMS incorporates information to support the use of Actemra at doses of 10 mg/kg for pediatric patients < 30 kg and 8 mg/kg for pediatric patients ≥ 30 kg given once every 4 weeks for the new proposed indication in the treatment of P-JIA. The goal and REMS elements are unchanged. The proposed REMS modification includes revision to the appended REMS materials, specifically, the *Dear Healthcare Professional letter* and the *journal information pieces* to include the new proposed indication in P-JIA and recommended dosage and administration described above.

The sponsor submitted a proposed REMS modification (received on April 2, 2013) with revisions to the Prescriber Education Slide Deck and the REMS Document in response to review of the 3-year REMS assessment and comments from the Agency (sent on March 5, 2013). A subsequent DRISK review will address that proposed REMS modification for Actemra.

1.1 BACKGROUND

Tocilizumab (Actemra) is a monoclonal antibody of the IgG₁ subclass that binds to interleukin-6 (IL-6) receptor, thereby inhibiting the biologic activity of IL-6. Interleukin-6 is a cytokine that is an important mediator of inflammation, including the production of acute phase reactants.

Actemra was approved on January 8, 2010 for the treatment of moderately to severely active Rheumatoid Arthritis in adult patients and on April 15, 2011 for the treatment of active systemic idiopathic juvenile arthritis (S-JIA) in pediatric patients 2 years and older.

Prior DRISK reviews include the background, and regulatory history of the original REMS and REMS modifications for Actemra.^{2, 3, 4, 5, 6}

¹ Serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies.

² DRISK Final REMS Modification for Actemra, written by Carolyn L. Yancey, M.D., on April 6, 2011

³ DRISK MEMORANDUM to the Final REMS Modification for Actemra written by Carolyn L. Yancey, M.D., on April 13, 2011

1.2 REGULATORY HISTORY

The regulatory history specific to this proposed modification to the REMS for Actemra (Efficacy supplement submitted on June 28, 2012; Supplement 064) follows:

- January 25, 2012: (Biologic IND 011-972) Hoffman-La Roche requested a Type B, pre-sBLA meeting for Actemra and the proposed treatment of P-JIA
- March 9, 2012: The sponsor sent the Agency background materials including questions about Actemra in p-JIA
- April 30, 2012: An internal DPARP meeting was held (including the DRISK) to discuss the format and plans for sBLA for Actemra in P-JIA. The DRISK responded to two questions about the approved Actemra REMS and timing of a subsequent REMS assessment
- May 1, 2012: (BB-IND 011-972) The Agency sent written responses to the sponsor's questions in the pre-sBLA Actemra/P-JIA meeting package
- June 28, 2012: The applicant submitted efficacy supplement 064 that includes a proposed amendment to the REMS modification for Actemra for the propose indication in P-JIA.
- October 11, 2012: The Agency approved the third REMS Modification for Actemra. Revisions include a new *Prescriber Education Slide Deck* to enhance prescriber understanding about specific safety risks with Actemra based on the prescriber survey results in last REMS assessment.
- January 7, 2013: The sponsor submitted the 3-year REMS assessment for Actemra to the Agency. The 3-year REMS assessment will not affect the DRISK responses to Supplement 064, subject of this review.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following material, listed by document date, reviewed from sBLA 125-276 (Supplement 064) for the proposed amendment to the Actemra REMS Modification, is:

- June 28, 2012: Proposed REMS Modification for Actemra submitted with efficacy supplement 064 that incorporates the proposed indication in P-JIA

⁴ DRISK Required Amendments to a REMS Modification based on a REMS Assessment Review written by Carolyn L. Yancey, M.D., on November 10, 2011

⁵ DRISK Review of Final Amendment to the REMS Modification Proposed for Actemra written by Carolyn L. Yancey, M.D. on June 8, 2012

⁶ DRISK Final Review of Amendments to the Proposed REMS Modification for Actemra written by Carolyn L. Yancey, M.D. on October 3, 2012

2.2 ANALYSIS TECHNIQUES

The applicant's proposed modification to the Actemra REMS (received on June 28, 2012) incorporates the proposed indication in P-JIA to specific appended REMS materials and a minor edit to the header of the REMS Document to insert the most recent modification date. Review of the proposed indication is based on the clinical efficacy and safety review from the DPARP.⁷

3 RESULTS OF REVIEW OF THE PROPOSED MODIFICATION TO THE REMS FOR ACTEMRA

The applicant's proposed modification to the Actemra REMS incorporates the proposed indication for treatment of P-JIA to specific appended REMS materials. The REMS Document requires minor revision to include the Most Recent Modification date in the header. The REMS elements are unchanged as no new observed safety risks are in the pediatric clinical trials conducted under supplement 064.

The target prescribers for the communication plan are unchanged and include pediatric rheumatologists based on the approved indication in S-JIA. The applicant's proposed revisions to specific appended REMS materials follow:

- *Dear Healthcare Provider letter*
 - Informs prescribers that there are *three indications* for Actemra (RA, P-JIA and S-JIA) versus two indications
 - Inserts the proposed indication: "Children 2 years of age and older with active Polyarticular Juvenile Idiopathic Arthritis (PJIA) with a recommended ACTEMRA dosing interval of every 4 weeks."
 - Under **Important Safety Information on Known and Potential Risks:**
 - **Gastrointestinal Perforations:** inserts minor correction to clarify 6-month clinical trials in RA
 - Under **Important Safety Information on Laboratory Abnormalities:**
 - In the sentence, "While on Actemra, liver aminotransferases (ALT, AST), neutrophil counts, and platelet counts should be measured every 4 to 8 weeks for RA, *inserts "and P-JIA"* at the time of the second infusion and, thereafter, every 2 to 4 weeks for S-JIA "
 - In the sentence, "Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter for RA, *inserts P-JIA,* and S-JIA.
- *Journal Information Pieces*

⁷ Clinical Review for Tocilizumab in Polyarticular Juvenile Idiopathic Arthritis written by Nikolay P. Nikolov, M.D., DPARP, on March 25, 2013

- Inserts the proposed new indication in *P-JIA and recommended dosing*, where appropriate
- Inserts the earlier described edit to the **Gastrointestinal Perforations** section of the Important Safety Information regarding Actemra, added where appropriate
- *REMS Website for Actemra*
 - The ACTEMRA REMS website landing page is acceptable. The links in the landing page must be up-dated to include the revised appended REMS materials.

See the **Attachments** to this review for clean versions of the proposed revisions to the REMS Document and specific appended REMS materials.

4 DISCUSSION AND CONCLUSION

The applicant's proposed modification to the Actemra REMS (received on June 28, 2012) is based on the efficacy supplement 064 proposed for the treatment of P-JIA in children age 2 years and older. The DPARP agrees with the applicant's proposed changes. There are no new safety risks observed in the P-JIA clinical trials (see the Clinical Review written by Nikolay P. Nikolov, M.D., DPARP, dated March 25, 2013).

The proposed minor revision in the REMS Document to update the most recent modification date in the header is acceptable. The proposed revisions to the appended REMS materials to incorporate the new proposed indication for children 2 years of age and older with active P-JIA with a recommended dosing interval of every 4 weeks, and minor edits to specific safety sections of the DHCP letter and specific journal information pieces are acceptable to the DPARP and the DRISK.

The REMS supporting document is revised to include the proposed indication in P-JIA and updated regulatory history that includes this efficacy supplement. The REMS assessment plan is included in the REMS supporting document (received on June 28, 2012) and remains unchanged from the most recent REMS modification (dated October 11, 2012).^{2, 3, 4, 5, 6} The REMS assessment plan will be included in the Efficacy Supplement Approval letter following completion of all required revisions.

5 RECOMMENDATIONS

The DRISK recommends approval of the proposed modification to the Actemra REMS based on the proposed indication in P-JIA summarized in **Sections 3 and 4**, of this review. To the DPARP, please send the comments in Section 6, in this review, to the applicant in a REMS Correspondence letter and copy the DRISK on this written communication.

6 COMMENTS TO BE SENT TO THE SPONSOR

The proposed modification to the Actemra REMS (supplement 064 received on June 28, 2012) based on a new proposed indication in P-JIA is acceptable to the Agency.

See the following comments below:

1. The REMS website landing page is acceptable as submitted. You must update the links in the landing page to include the revised appended REMS materials.
2. You are reminded that the REMS Supporting Document must be consistent with the REMS Document (see the **Attachment**)

ATTACHMENTS

REMS Document and Appended REMS materials

Initial REMS Approved: 01/08/2010

Most Recent Modification: XX/XX/2012

BLA 125276 ACTEMRA® (tocilizumab)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080

I. GOALS

The goal of the ACTEMRA REMS is:

- To inform healthcare providers about the serious risks associated with ACTEMRA.

II. REMS ELEMENTS

A. Communication Plan (FDCA Section 505-1(e)(3))

In accordance with FDCA 505-1(e)(3), Genentech, A Member of the Roche Group, will implement a communication plan to the following adult and pediatric healthcare providers:

- Rheumatologists and rheumatology healthcare providers who are likely to prescribe ACTEMRA
- Infectious disease specialists who may be consulted about serious infection
- Gastroenterologists and hepatologists who may be consulted about gastrointestinal perforation, hepatic disease, or hepatic impairment

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/s/

CAROLYN L YANCEY

04/09/2013

Review of the proposed modification to the REMS for Actemra based on the proposed indication in polyarticular JIA

CLAUDIA B MANZO

04/09/2013

concur

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

OTHER REVIEW(S)

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY DRUG PRODUCTS

Labeling Review for Actemra BLA Supplement # 64

BLA: 125276, Supplement # 64

Drug: Actemra, Monoclonal antibody to IL-6 receptor

Date submitted: June 28, 2012

Review completion date: April 18, 2013

Sponsor: Genentech

Reviewer: Asoke Mukherjee Ph.D

Regulatory background:

Tocilizumab is a monoclonal antibody for the IL-6 receptor approved for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. A new efficacy supplement (# 64) was submitted for the Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age or older. The sponsor submitted clinical efficacy and safety data for a 24-week randomized double-blind trial with a 80 week open label extension. The dose studied was 10 mg/kg/IV for patients less than 30 kg and 8 mg/kg/IV for patients above 30 kg body weight given every 4-week intervals. No non-clinical data were submitted for the efficacy supplement because non-clinical pharmacology and toxicology studies were reviewed under the original BLA that was approved on January 8, 2010. No changes to nonclinical portions of the product label (i.e., sections 8, 11, 12 and 13) are needed for the present efficacy supplement.

However, following a review of the proposed product label, the CDER labeling review team (SEALD Team) on April 15, 2013 requested clarification of the established pharmacological class (EPC) for Tocilizumab. Further, the team noted that Tocilizumab was not present in the eList (<http://elist/prpllr/public/query/>); the EPC should be confirmed and Tocilizumab should be added to the list. EPC be determined before approval as per FDA guidelines of the proposed label. Following a discussion of the EPC with Dr. Paul Brown, the Associate Director, Pharmacology/Toxicology, by email on April 17, 2013, a change was recommended from interleukin-6 receptor “inhibitor” (in the current label) to interleukin-6 receptor “antagonist” (in the revised label). Therefore, the present description of Actemra under the Indications and Usage Section of the product label should state that Actemra (Tocilizumab) is an IL-6 receptor antagonist. Accordingly, the following change in the label is recommended from the non-clinical perspective for the product label

Recommended label:

-----INDICATIONS AND USAGE -----
ACTEMRA[®] (tocilizumab) is an interleukin-6 (IL-6) receptor ~~inhibitor~~ antagonist

Recommendations:

Approval of the efficacy supplement from the non-clinical perspective is recommended. Product labeling should be changed as recommended above. Dr. Paul Brown will add Tocilizumab to the eList.

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/s/

ASOKE MUKHERJEE
04/18/2013

TIMOTHY W ROBISON
04/18/2013
I concur



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center

FINAL LABEL AND LABELING REVIEW

Date: April 12, 2013

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products

Through: Gerry Feldman, Ph.D.
Division of Monoclonal Antibodies

Patrick Swann
Deputy Director
Division of Monoclonal Antibodies

Application: BLA 125276/64

Product: Actemra (tocilizumab)

Applicant: Genentech Inc.

Submission Date(s): June 28, 2012

Executive Summary

The carton and container labels for Actemra (tocilizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, USP 35/ NF 30 (12/1/12-5/1/13). Labeling deficiencies were not identified. Comments are listed in the conclusions section. The label and labeling submitted on June 28, 2012 are acceptable.

Background and Summary Description

The purpose of this supplemental is to provide data in support of the use Actemra at the doses of 10 mg/kg for patients < 30 kg and 8mg/kg for patients \geq 30 kg given once every

4 weeks for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

Materials Reviewed:

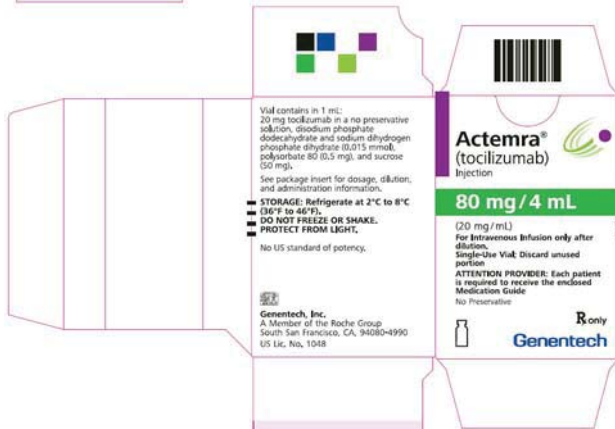
<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680f59cf8>

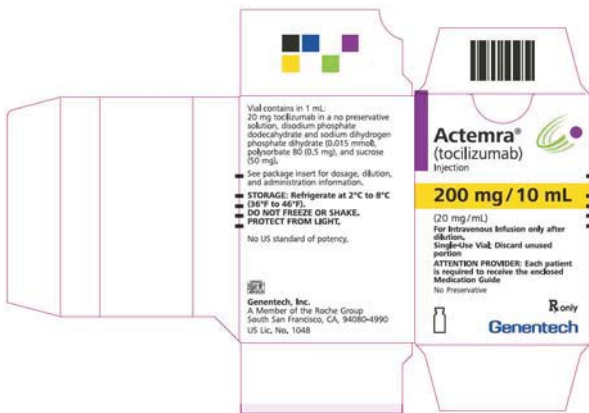
Sequence: 0097

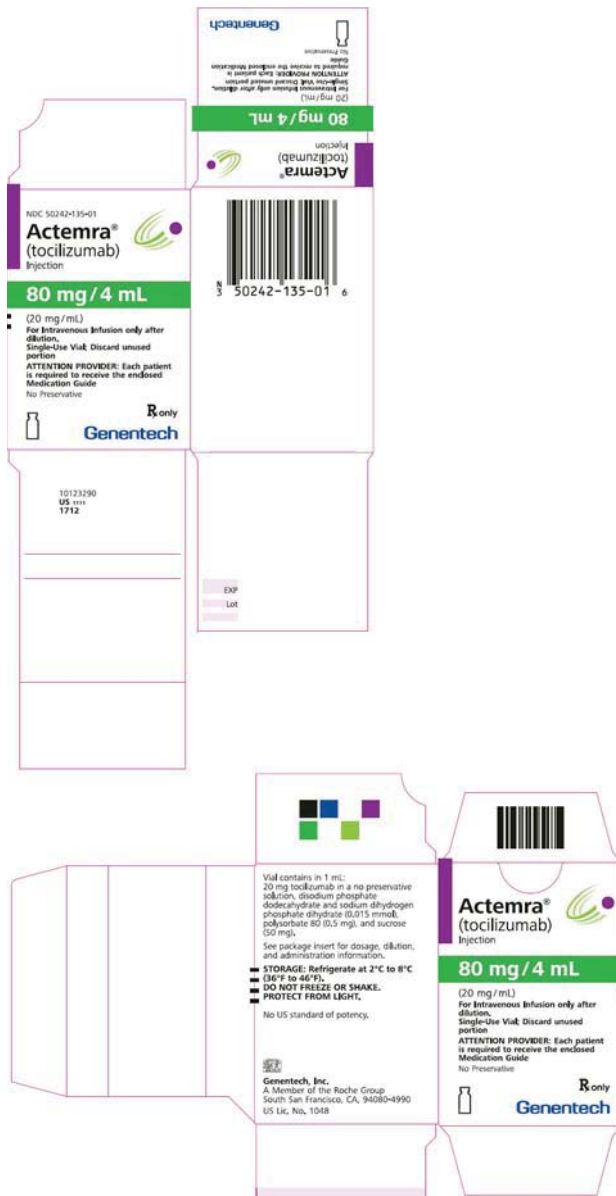
Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

Start of Sponsor Material

Appears This Way On Original







End of Sponsor Material

Conclusions

Actemra was originally approved January 8, 2010 with three strengths a) 80 mg per 4 mL b) 200 mg per 10 mL c) 400 mg per 20 mL. The labels were also approved in single vial and a 4 vial carton configuration. However, the 4 vial carton was never commercialized according to an email from Genentech dated March 20, 2012 from Stuart Heminway and is not included in this submission for consideration. The submitted single vial configurations labels submitted June 28, 2013 are identical to the originally approved labels and are acceptable.

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/s/

KIMBERLY M RAINS
04/12/2013

GERALD M FELDMAN
04/15/2013

PATRICK G SWANN
04/15/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	ACTEMRA (tocilizumab) injection, for intravenous use
Applicant	Genentech
Application/Supplement Number	BLA 125276/S-64
Type of Application	Efficacy Supplement
Indication(s)	Treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis
Established Pharmacologic Class ¹	Interleukin-6 (IL-6) receptor inhibitor
Office/Division	ODE II/DPARP
Division Project Manager	Philantha Bowen
Date FDA Received Application	June 29, 2012
Goal Date	April 29, 2013
Date PI Received by SEALD	April 11, 2013
SEALD Review Date	April 15, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *The margin on the left side and between columns is < 1/2 inch along the sides of the Boxed Warning.*

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: *White space is absent prior to the Indications and Usage section.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The "Administration" subheading under D&A does not have references.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- NO** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment: *The appropriate dates must be stated.*

- NO** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *The RMC from 10/2012 are within a year of anticipated approval of this ES and must be included.*

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Selected Requirements of Prescribing Information

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *The title must be bolded.*

- NO** 32. All section headings must be **bolded** and in UPPER CASE.

Selected Requirements of Prescribing Information

Comment: *The section headings must be bolded.*

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment: *Subsection 1.3 is not indented.*

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

NO 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment: *A period must be placed at the end of the statement.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Selected Requirements of Prescribing Information

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: Outer brackets are missing in multiple places in subsection 5.3 where referencing subsection 2.5.

NO

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: Vertical lines are absent.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES

42. All text is **bolded**.

Comment:

YES

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

NO

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *This statement should be the first statement under subsection 6.1. Also, the statement has been modified, which is allowed, however, the phrase "broader patient population" has been added; it is up to the review division's discretion to determine if this is acceptable.*

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

ELIZABETH A DONOHOE
04/15/2013

LAURIE B BURKE
04/15/2013



Date: March 4, 2013
From: Gerald M. Feldman, Ph.D.
Laboratory of Molecular and Developmental Immunology
Division of Monoclonal Antibodies, CDER
Through: Marjorie A. Shapiro, Ph.D., Chief, LMDI
Subject: Assessment of immunogenicity assays used in Study WA 19977
To: **BLA 125276/64 (File)**

Therapeutic Agent(s): Tocilizumab (Actemra[®]), a humanized antibody to IL-6R.

Clinical Indication(s): Rheumatoid Arthritis

Manufacturer(s): Chugai, Inc. and Genentech Inc
Utsunomiya, Japan South San Francisco, CA

Sponsor: Genentech, Inc.

Contact: Kristine Ogozalek
Regulatory Affairs
(973) 235-6227

Date of Submission: 125276/64 June 29, 2012
125276/64.2 September 13, 2012

Executive Summary:

This efficacy supplement provides additional clinical data (WA 19977) for Actemra in support of a new indication, pJIA. On August 29, 2012, the Sponsor received a request to describe any differences between the immunogenicity assay as described in the Original BLA (125276.00) for Actemra for RA, and the current supplement. 125276/64.2 provides the requested validation data and study reports for the immunogenicity assay used in study WA19977.

All notes and comments by reviewer are in italicized font.

Background

Tocilizumab (Actemra) was licensed in October, 2010 for the treatment of patients with rheumatoid arthritis (BLA 125276.00). On June 28, 2012 Hoffmann-La Roche submitted BLA supplement 125276.64 to expand the indication of tocilizumab for the treatment of patients 2 years of age and older who are suffering from polyarticular Juvenile Idiopathic Arthritis (pJIA). During the course of review for this supplement, a question arose as to the nature of

the immunogenicity assays used in the studies for pJIA, and how they compared to the immunogenicity assays used in the original clinical trials. The Sponsor was asked to provide these data, and the current submission addresses this issue.

Assessment

Three distinct assays are used in determining immunogenicity: screening, confirmation, and neutralization. The tables below (copied from submission) compare the assays used in support of clinical study 19977 to those previously submitted in support of the original BLA:

Table 1 Comparison of assays used in original BLA (125276) and pJIA sBLA (125276/64)

Assay	Original BLA (analysis done at (b) (4))		pJIA (analysis done at (b) (4))		Differences between Method performed at (b) (4) as compared to (b) (4)
	Validation Report Title	Validation Report Number	Validation Report Title	Validation Report Number	
Immunogenicity Assay					
Anti-Tocilizumab Antibody Screening and Confirmation Assay	Validation of an Immunoassay Method for the Measurement of Anti-MRA Antibodies in Human Serum - Screening and Confirmatory Assay - (b) (4)	1025410	Validation of an Immunoassay Method for the Determination of Anti-Tocilizumab (TCZ) Antibodies in Human Serum Samples - Screening and Confirmation Assay - (b) (4)	1039804	<p>The anti-Tocilizumab antibody screening assay at (b) (4) was similarly sensitive as at (b) (4) with estimated cut-point sensitivities of 50.8 ng/mL (Healthy Volunteers) and 123 ng/mL (Rheumatoid Arthritis Patients).</p> <p>In study WA19977 (pJIA patient population), the cut-point was based on a cut-point factor determined from Healthy Volunteers instead of RA patients.</p> <p>(b) (4) established additional freeze/thaw stability for the Positive Control antibody, for a total of 10 F/T cycles, in contrast to 5 F/T cycles in the validations at (b) (4)</p> <p>There are minor differences in the numerical values documented for validation parameters (e.g. precision, accuracy, recovery), but these subtle differences do not affect the results.</p> <p>Performance Summary see Table 2</p> <p>Performance Summary of the Anti-Tocilizumab Antibody Screening and Confirmation Assay Table 2 below.</p>
	Validation of an Immunoassay Method for the Measurement of Anti-MRA (RO4877533) Antibodies in Human Serum - Screening and Confirmatory Assay - (b) (4)	1025358			

Assay	Original BLA (analysis done at (b) (4))		pJIA (analysis done at (b) (4))		Differences between Method performed at (b) (4) as compared to (b) (4)
	Validation Report Title	Validation Report Number	Validation Report Title	Validation Report Number	
Anti-Tocilizumab Antibody (neutralizing) Assay (Inhibition ELISA)	Validation of an Immunoassay Method for the Measurement of Neutralizing Anti-MRA Antibodies in Human Serum - Inhibition Assay - (b) (4)	1025570	Validation of an Immunoassay Method for the Determination of Neutralizing Anti-Tocilizumab (TCZ) Antibodies in Human Serum Samples - Inhibition Assay - (b) (4)	1038442	<p>At (b) (4) the lower and upper limits of quantification were set to match those validated at (b) (4) (211 ng/mL and 2400 ng/mL).</p> <p>At (b) (4) intra-assay precision ranged from 6.1 % to 38.9 %, and inter-assay precision ranged from 4.3 % to 35.9 %. However, the high maximal values were obtained at a QC level outside the utilized quantification range (at 175 ng/mL).</p> <p>Recovery determined from RA serum was lower (59.0%), in contrast to 105.9% (b) (4) and 114.2% (b) (4).</p> <p>(b) (4) established additional freeze/thaw stability of the Positive Control antibody for a total of 10 F/T cycles, in contrast to 5 F/T cycles in the validations at (b) (4).</p> <p>There are minor differences in the numerical values documented for validation parameters (e.g. precision, accuracy, recovery), but these subtle differences do not affect the results.</p> <p>Performance Summary see Table 3 below.</p>
	Validation of an Immunoassay Method for the Measurement of Neutralizing Anti-MRA (RO487533) Antibodies in Human Serum - Inhibition Assay - (b) (4)	1025483			

The Sponsor asserts that the immunogenicity assays performed for pJIA are essentially the same as those previously submitted in the original BLA. The original assays were conducted at (b) (4) and at (b) (4). Those validated assays were later transferred to and established at (b) (4) (b) (4) which conducted the analyses for study WA19977. The re-validation for all of these assays was performed at (b) (4), and their study reports are provided as part of the current submission (Module 5-3-5-4). The validation reports were reviewed.

Reviewer's comment:

The data provided in the validation reports demonstrate that the immunogenicity assays used for the pJIA study were qualitatively similar to those previously validated in BLA 125276.00 and used for the RA studies. There were some minor quantitative differences among the assays in terms of their performance characteristics, due to inherent variability in inter- and intra-assay precision. These differences can be visualized in the tables below (copied from submission):

Table 2 Performance Summary of the Anti-Tocilizumab Antibody Screening and Confirmation Assay

Validation Site	Assay Range, ng-equiv./mL	Screening Cut-point Sensitivity, ng-equiv./mL	Accuracy, %		Precision, %	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
(b) (4)						

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

Table 3 Performance Summary of the Inhibition ELISA

Validation Site	LLOQ, ng-equiv./mL	Assay Range, ng-equiv./mL	Accuracy, %		Precision, %	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
(b) (4)						

Some of the differences noted (e.g. assay range) provide an advantage to the (b) (4) assay. None of the observed differences in assay performance can be considered to significantly affect the overall results of the study. Similar to what was observed in the initial assay validations, determination of anti-product antibodies are affected by low (1 µg/ml) concentrations of Actemra, necessitating the need to collect serum samples during trough periods in order to avoid false positive results. Serum samples were indeed collected at trough (28 day intervals), at which time serum Actemra levels were below 0.7 µg/ml (for pts < 30 kg, slightly higher in pts > 30 kg). Assay validation results also demonstrated that for low anti-drug antibody (ADA) concentrations, the presence of 0.1 µg/ml sIL-6R in the sample is sufficient to interfere with the assay, though at higher ADA concentrations no interference is observed at sIL-6R concentrations up to 1.0 µg/ml.

It is the conclusion of this reviewer that the assays used to determine immunogenicity for Study 19977 are not inherently different than those previously used during the licensure of Actemra for the treatment of RA.

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/s/

GERALD M FELDMAN
03/28/2013

MARJORIE A SHAPIRO
03/28/2013

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

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

Memorandum

Date: March 14, 2013

To: Philantha Bowen, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matthew Falter, Regulatory Review Officer
Roberta Szydlo, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Acting Group Leader, OPDP

Subject: BLA 125276/S-064
OPDP labeling comments for ACTEMRA[®] (tocilizumab) Injection,
for intravenous infusion

In response to DPARP's consult request dated August 9, 2012, OPDP has reviewed the revised proposed Package Insert (PI), Carton/Container labeling, and Medication Guide (MG) for ACTEMRA[®] (tocilizumab) Injection, for intravenous infusion (Actemra).

Reference is made to OPDP's previous labeling comments for Actemra dated March 29, 2011; December 10, 2010; and February 5, 2008.

This supplement provides for an additional indication for Actemra. Specifically, S-064 provides for adding the treatment of polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older to Actemra's approved indications. OPDP's review of the PI and MG is limited to the changes associated with the addition of the PJIA indication only.

OPDP's comments on the PI and MG are based on the proposed draft marked-up labeling titled "BLA 125276(64) – DPARP Label-tracked.doc" that was sent via email from DPARP to OPDP on March 4, 2013 (attached below for reference). OPDP has no comments on the proposed PI or MG at this time.

OPDP has also reviewed the Carton/Container labeling submitted by the sponsor and located in the EDR at:

- \\cber-fs3\M\leCTD_Submissions\STN125276\0097\m1\us\114-label\114-1-draft-label\114-1-3-draft-label-text\spl\actemra-03.jpg
- \\cber-fs3\M\leCTD_Submissions\STN125276\0097\m1\us\114-label\114-1-draft-label\114-1-3-draft-label-text\spl\actemra-02.jpg

We have no comments at this time on the proposed Carton/Container labeling.

OPDP appreciates the opportunity to provide comments on the proposed labeling.

If you have any questions concerning the PI or Carton/Container labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

If you have any questions concerning the MG, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

Following this page 33 pages have been withheld in full due to draft labeling (b) (4)

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

/s/

ROBERTA T SZYDLO
03/14/2013

MATTHEW J FALTER
03/14/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: March 12, 2013

Reviewer(s): Teresa McMillan, PharmD
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, PharmD
Division of Medication Error Prevention & Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention & Analysis

Drug Name(s) and Strength(s): Actemra (Tocilizumab)
Injection
80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL

Application Type/Number: BLA 125276

Submission Number: 64

Applicant/sponsor: Genetech

OSE RCM #: 2012-1860

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed insert labeling and medication guide for Actemra (Tocilizumab), BLA 125276 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Actemra (Tocilizumab) was approved on January 8, 2010 for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) and on April 15, 2010 for Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years and older. On June 28, 2012, the Applicant submitted an efficacy supplement for the proposed indication of active Polyarticular Juvenile Idiopathic Arthritis (PJIA) in patients 2 years and older.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 28, 2012 proprietary name submission.

- Active Ingredient: Tocilizumab
- Indication of Use: Rheumatoid Arthritis (RA), Systemic Juvenile Idiopathic Arthritis (SJIA), Polyarticular Juvenile Idiopathic Arthritis (PJIA)
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL
- Dose and Frequency:
 - i) RA- 4 mg/kg once every 4 weeks followed by an increase to 8 mg/kg once every 4 weeks based on clinical response.
 - ii) PJIA-10 mg/kg once every 4 weeks if patient less than 30 kg or 8 mg/kg once every 4 weeks if patient is at or above 30 kg.
 - iii) SJIA-12 mg/kg once every 2 weeks if patient less than 30 kg or 8 mg/kg once every 2 weeks if patient is at or above 30 kg.
- How Supplied: Sterile concentrate, preservative-free single-use vial (20 mg/mL) solution for intravenous infusion. Supplied individually or in box of 4 single-use vials.
- Storage: Refrigerated at 2°C to 8°C (36° to 46° F). Do not freeze. Store in the original container to protected from light.

2 METHODS AND MATERIALS REVIEWED

2.1 LITERATURE SEARCH

We searched PubMed and the ISMP publications on for additional cases and actions concerning Actemra. No additional cases were identified.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling and Medication Guide submitted on November 7, 2012 (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Actemra in OSE Label and Labeling Review #2010-2255 which evaluated the addition of Systemic Juvenile Idiopathic Arthritis indication. We looked at the review to ensure all our recommendations were implemented. In addition, DMEPA completed a FDAAA Section 915 New Molecular Entity (NME) Postmarketing Safety Evaluation (#2010-601 dated March 5, 2013) for Actemra. In our review we identified and evaluated the following medication errors: wrong dose [overdose] (n=7), incorrect administration time (n=2), wrong route (n=2), and incorrect preparation of drug (n=2). No root cause or outcome was reported for any of these errors.

We reviewed the Prescribing Information and assessed the dosing and administration time, route of administration, as well as the dilution steps. Also, the labels and labeling prominently display the route of administration. We also note that the total drug content and the amount of drug per milliliter are prominently displayed on the carton labeling and the container label. The Prescribing Information, carton labeling, and the container labels appeared adequate to help mitigate the medication errors observed. Thus, no label and labeling recommendations were made in the 915 safety evaluation.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESMENT OF PROPOSED INDICATION

The Applicant is proposing a new indication of active Polyarticular Juvenile Idiopathic Arthritis (PJIA) in patients 2 years and older. The proposed dose and frequency of PJIA is 10 mg/kg once every 4 weeks if the patient is less than 30 kg or 8 mg/kg once every 4 weeks if patient is at or above 30 kg. The Applicant is proposing to use the currently approved 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL single-use vials for intravenous infusion. The currently approved formulation and strengths are adequate for use in administering the proposed dose of 10 mg/kg or 8 mg/kg. The medication guide sufficiently reflects the proposed changes. However, we noted the insert labeling can be further improved to clarify important information for the healthcare practitioner.

4 CONCLUSIONS

DMEPA concludes that the medication guide is acceptable. However, the proposed insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA supplement:

5.1 COMMENTS TO THE DIVISION

A. Insert labeling

1. In section 2.4, Step 1, replace the word “solution” with “injection”.
2. In section 2.4, Step 2, revise the statement “ Slowly add ACTEMRA for intravenous infusion from each vial into the infusion bag or bottle” to the following:

Slowly add the volume of ACTEMRA injection required for the patient’s dose into the infusion bag or bottle.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

TERESA S MCMILLAN
03/12/2013

LUBNA A MERCHANT
03/12/2013

SCOTT M DALLAS
03/13/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **March 11, 2013**

To: **Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy, Rheumatology Products
(DPARP)**

Through: **LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)**

**Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
DMPP**

From: **Sharon W. Williams, RN, BSN, MSN
Patient Labeling Reviewer
DMPP**

Subject: **DMPP Review of Patient Labeling: Medication Guide (MG)**

Drug Name (established name): **Actemra (tocilizumab)**

Dosage Form and Route: **Injection for Intravenous Infusion**

Application Type/Number: **BLA 125276**

Supplement Number: **S-64**

Applicant: **Hoffman-La Roche Incorporated**

1 INTRODUCTION

Actemra was originally approved on January 8, 2010, for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Original approved labeling included a Risk Evaluation and Mitigation Strategy (REMS) with a Medication Guide and Communication Plan. On April 15, 2011, the Medication Guide was removed from the REMS and was maintained as part of the approved labeling in accordance with 21 CFR 208.

On June 28, 2012, Hoffman-La Roche Incorporated submitted a new efficacy supplement for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older. On August 9, 2012 the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide for ACTEMRA (tocilizumab).

This memorandum documents the DMPP review and concurrence with the Applicant's proposed Medication Guide (MG) for Actemra (tocilizumab).

2 MATERIAL REVIEWED

- Draft ACTEMRA (tocilizumab) Injection for Intravenous Infusion MG received on June 28, 2012 and received by DMPP on March 4, 2013.
- Draft ACTEMRA (tocilizumab) Prescribing Information (PI) received on June 28, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 4, 2013.
- Approved ACTEMRA (tocilizumab) Injection for Intravenous Infusion labeling dated October 11, 2012.

3 CONCLUSIONS

The Applicant's proposed MG revisions are acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
03/11/2013

MELISSA I HULETT
03/11/2013

LASHAWN M GRIFFITHS
03/11/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 125276/64

Application Type: BLA efficacy supplement

Name of Drug: Actemra (tocilizumab), Injection for Intravenous Infusion

Applicant: Genentech, A Member of the Roche Group

Submission Date: June 28, 2012

Receipt Date: June 29, 2012

1.0 Regulatory History and Applicant's Main Proposals

The purpose of this sBLA is to provide data to support the use of Actemra for the treatment of polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. This sBLA submission also address the PREA PMR in the original approval letter dated January 8, 2010.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 60-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 12, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required

Selected Requirements of Prescribing Information (SRPI)

• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: The proposed label states **See 17 for PATIENT COUNSELING INFORMATION and (b) (4) Medication Guide.**”

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

Selected Requirements of Prescribing Information (SRPI)

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

Clearance: Jafari/8-10-12

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/s/

PHILANTHA M BOWEN
08/13/2012

LADAN JAFARI
08/18/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125276	NDA Supplement #:S- BLA Supplement # 64	Efficacy Supplement Type SE- 1
Proprietary Name: Actemra Established/Proper Name: tocilizumab Dosage Form: Injection (IV infusion) Strengths: 80mg/4ml; 200mg/10ml; 400mg/20ml		
Applicant: Genentech, A Member of the Roche Group Agent for Applicant (if applicable):		
Date of Application: June 28, 2012 Date of Receipt: June 29, 2012 Date clock started after UN:		
PDUFA Goal Date: April 29, 2013	Action Goal Date (if different):	
Filing Date: August 28, 2012	Date of Filing Meeting: August 6, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): <i>active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older</i>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 <i>and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 11972: (b)(4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>																				

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?				
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			✓	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	✓			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			✓	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			✓	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	✓			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	✓			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	✓			
<u>BPCA (NDAs/NDA efficacy supplements only):</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			✓	
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	✓			
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		✓		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 3/20/07	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 5/1/12	✓			Written Responses provided; no meeting
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): SPA granted 6/8/09; amended SPA granted 10/6/11 MtgMin 4/3/09	✓			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 6, 2012

BLA/NDA/Supp #: 125276/64

PROPRIETARY NAME: Actemra

ESTABLISHED/PROPER NAME: tocilizumab

DOSAGE FORM/STRENGTH: injection – 80mg/4ml; 200mg/10ml; 400mg/20ml

APPLICANT: Genentech, A Member of the Roche Group

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): polyarticular juvenile idiopathic arthritis

BACKGROUND:

The purpose of this sBLA is to provide data to support the use of Actemra for the treatment of polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. This sBLA submission also address the PREA PMR in the original approval letter dated January 8, 2010.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Philantha Bowen	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Sarah Yim		N
Clinical	Reviewer:	Nikolov Nikolay	Y
	TL:	Sarah Yim	N
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Elizabeth Shang	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Yongman Kim	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Asoke Mukherjee	Y
	TL:	Molly Shea	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for BLAs/BLA efficacy supplements)</i>	Reviewer:	Gerald Feldman	N
	TL:	Marjorie Shapiro	N
Product Quality (CMC)	Reviewer:	Gerald Feldman	N
	TL:	Marjorie Shapiro	N
Quality Microbiology <i>(for sterile products)</i>	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<p>Comments:</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: The efficacy data for this product has been reviewed during the original BLA review for which an OSI audit was conducted.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul A. Chowdhury	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	<p>filing letter; For NDAs/NDA supplements: see CST for choices)</p> <ul style="list-style-type: none"> • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

PHILANTHA M BOWEN
08/13/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125276Orig1s064

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 125276	BLA Supplement # 64	If NDA, Efficacy Supplement Type:
Proprietary Name: ACTEMRA Established/Proper Name: Tocilizumab Dosage Form: Intravenous use		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Philantha Montgomery Bowen		Division: DPARP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 29, 2013</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input checked="" type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	April 29, 2013
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP: April 29, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4/29/13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	6/28/12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4/29/13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	6/28/12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	6/28/12: FPL submitted; no changes
<ul style="list-style-type: none"> • Most-recent draft labeling 	N/A
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	N/A
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 8/13/12 <input checked="" type="checkbox"/> DMEPA 3/13/13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 3/11/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 3/14/13 <input checked="" type="checkbox"/> SEALD 4/15/13 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews – OBP 4/15/13; Nonclin – 4/18/13
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	8/13/12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>2/6/13</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	4/29/13; 4/22/13; 4/17/13 (2); 4/16/13; 4/9/13; 3/28/13; 1/15/13; 8/28/12; 7/30/12
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg <i>Written responses provided – 5/1/12</i>
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 3/20/2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	<i>SPA meeting - 3/5/2009</i>
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None April 29, 2013
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None April 8, 2013
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 1
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	<i>Refer to CDTL memo 4/8/13</i>
• Clinical review(s) <i>(indicate date for each review)</i>	3/25/13; 8/7/12
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	Clinical review, pg. 21, 3/25/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i>	6/28/12
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input type="checkbox"/> None Review - 4/9/13; 4/25/13

⁶ Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None See concurrence on primary review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/20/13; 8/7/12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None See concurrence on primary review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 3/25/13; 8/22/12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/1/13
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None See concurrence on primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 3/28/13
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	3/19/13
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: 4/19/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

PHILANTHA M BOWEN
04/29/2013

Bowen, Philantha

From: Stuart Heminway [heminway.stuart@gene.com]
Sent: Monday, April 29, 2013 11:06 AM
To: Bowen, Philantha
Cc: Stuart Heminway
Subject: Re: sBLA 125276/64 - FDA Request for Labeling Revisions: Editorial Changes

Hi Philantha,

We confirm receipt of the editorial changes in the attached email and we agree.

Thank you and please let me know if you need anything else from me.

Best regards,
Stu

On Mon, Apr 29, 2013 at 7:24 AM, Bowen, Philantha <Philantha.Bowen@fda.hhs.gov> wrote:
Hello Stuart,

Your labeling submission dated April 19, 2013, to sBLA 125276/64 is currently under review. We have the following request for minor editorial revisions for the package insert. Following review if you agree to these recommendations, respond via email to this request with your agreement. Insertions are underlined in red font below.

Full Prescribing Information**Section 14 CLINICAL STUDIES**

- On page 23 of the package insert in the last paragraph within the *Clinical Response* subsection, revise to read:

"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."

Contact me if you have any questions.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Program Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10905 New Hampshire Ave, Bldg 22, Room 3316
Silver Spring, MD 20993
☎ [301-796-2466](tel:301-796-2466)

☎501-796-9718

✉philantha.bowen@fda.hhs.gov

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--

Stuart Heminway
Regulatory Program Director

Genentech, Inc, *A Member of the Roche Group*
1 DNA Way, Building 32, MS 241a
South San Francisco, CA 94074

Tel: 650-467-8460 / Mobile: (b) (6)
heminwas@gene.com

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/s/

PHILANTHA M BOWEN
04/29/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: A long-term safety study in 400 pediatric patients 2-17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of 400 pediatric pJIA patients treated with other biologics as standard of care. Patients should be followed for 5 years

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>February 2014</u>
	Study/Trial Completion:	<u>September 2022</u>
	Final Report Submission:	<u>April 2023</u>
	Other: <u>N.A.</u>	<u></u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The risk:benefit profile of tocilizumab in PJIA appears to be favorable based on the data in this supplement. The risks of tocilizumab treatment in this patient population appear to be qualitatively similar as those seen in adults with RA; with the primary serious risk being an increased risk of infection. Abnormalities in hepatobiliary, hematologic, and lipid parameters were also observed in PJIA patients; however, as with adults, these abnormalities did not appear to be correlated with clinical adverse events.

However, the risks of tocilizumab are not minimal, and IL6 has physiological functions in immune, reproductive, and skeletal system development. Therefore to ensure the long-term risk-benefit profile of tocilizumab in PJIA remains favorable, safety should be further assessed by a long-term safety registry with inclusion of a reference group, to assess for malignancies, serious infections, gastrointestinal perforation, and effects on growth and development.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

1) Actemra (tocilizumab) is labeled for an increased risk of serious infections and gastrointestinal perforation in adults. Additional long-term data are required to assess these known serious risks as they pertain to the use of Actemra in PJIA patients.

2) IL6 has important functions in the immune system and developing musculoskeletal system. Actemra (tocilizumab), as an IL6 inhibitor, has the potential for serious risks such as malignancy or adverse effects on bone development.

Additional long-term data are required to assess these potential risks as they pertain to the use of Actemra in PJIA patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is planned as an observational cohort study to evaluate long-term safety in pediatric patients 2-17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of 400 pediatric pJIA patients treated with other biologics as standard of care. Patients should be followed for 5 years.

Required

- Observational pharmacoepidemiologic study
- X Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- X Has the applicant adequately justified the choice of schedule milestone dates?
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
04/29/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

ELECTRONIC TRANSMITTAL SHEET

DATE: April 22, 2013

To: Stuart Heminway, Program Director Regulatory Affairs	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Genentech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Email: Heminway.stuart@gene.com	
Phone number: 650-467-8460	Phone number: 301-796-2466

Subject: BLA 125276/64 **Re: REMS Assessment Information Request**

Total no. of pages including cover: 3

Comments: Please Acknowledge Receipt: **TIME SENSITIVE**

Document to be mailed: YES NO

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BLA 125276/64
Actemra (tocilizumab)
Genentech

Dear Mr. Heminway:

Your submission dated June 28, 2012, to sBLA 125276/64 is currently under review and we have a request for a targeted REMS Assessment.

The targeted REMS assessment should include but not be limited to the following:

- A discussion on how the current REMS is functioning.
- A discussion of the REMS modification under this supplement.
- The impact of the additional information added to the REMS documents - e.g. is there a change in the benefit/risk with the new indication that would necessitate additional modification to the REMS.
- The impact of the modification on any future REMS assessments.

We request that you submit a response by COB Tuesday, April 23, 2013, officially to the sBLA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

BLA 125276/64
Actemra (tocilizumab)
Genentech

Drafted: Bowen/4-22-13

Clearance: Jafari/4-22-13
Seymour/4-22-13

Finalized: Bowen/4-22-13

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/s/

PHILANTHA M BOWEN
04/22/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

BLA#: 125276 Supplement Number: 64 NDA Supplement Type (e.g. SE5): SE1
Division Name: DPARP PDUFA Goal Date: 4/29/13 Stamp Date: 6/28/12
Proprietary Name: Actemra
Established/Generic Name: tocilizumab
Dosage Form: Intravenous Infusion
Applicant/Sponsor: Genentech, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) Rheumatoid Arthritis
 - (2) Systemic Juvenile Idiopathic Arthritis
 - (3) _____
 - (4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: 125276 Supplement #: _____ PMR #: 1

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>2</u> yr. <u>0</u> mo.	<u>16</u> yr. <u>11</u> mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum		maximum	
<input type="checkbox"/>	Neonate	__ wk. __ mo.		__ wk. __ mo.	
<input type="checkbox"/>	Other	__ yr. __ mo.		__ yr. __ mo.	
<input type="checkbox"/>	Other	__ yr. __ mo.		__ yr. __ mo.	
<input type="checkbox"/>	Other	__ yr. __ mo.		__ yr. __ mo.	
<input type="checkbox"/>	Other	__ yr. __ mo.		__ yr. __ mo.	
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.	

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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/s/

PHILANTHA M BOWEN
04/22/2013

**Therapeutic Biological Establishment Evaluation
Request (TB-EER) Form**
Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

Division Goal Date: April 22, 2013
PDUFA Action Date: April 29, 2013

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125276/64
Product(s): Actemra® (tocilizumab)

Short summary of application: *This is an efficacy supplement for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. This sBLA submission also address the PREA PMR in the original approval letter dated January 8, 2010.*

FACILITY INFORMATION

Manufacturing Location: Japan
Firm Name: Chugai Pharma Mfg. Co.
Address: 16-3 Klyohara Kogydanchi, Utsunomiya-city Tochigi, 321-3231,
Japan
FEI: 3006942691

Short summary of manufacturing activities performed: Drug substance and drug product manufacturing

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

This site was inspected by IOG on March 7 – 15, 2013. This inspection offered GMP coverage of Actemra drug product and drug substance manufacturing operations, and included coverage of the CBI and SVS profiles. The field recommendation for this inspection has been reviewed by DIDQ. On the basis of that review and discussion with the investigator, DIDQ does not oppose approval of this supplement from a GMP perspective. However, the approval of this supplement does not preclude the FDA from other actions related to the ongoing evaluation of this site.

Manufacturing Location: California

Firm Name: Genentech

Address: One Antibody Way, Oceanside, CA 92056-5802

FEI: 3006129086

Short summary of manufacturing activities performed: Drug Substance Manufacturing and Release Testing

This site was inspected by LOS-DO on September 2 – 15, 2010 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing and testing operations. The BTP and CTX profiles were updated following this inspection. Although the compliance status of this firm is out of date, a GMP inspection has been scheduled by LOS-DO for May 2013. This site is considered acceptable for the purposes of this supplement.

Manufacturing Location: California

Firm Name: Genentech

Address: 1 DNA Way, South San Francisco, CA 94080-4990

FEI: 2917293

Short summary of manufacturing activities performed: Virus and Mycoplasma Testing

This site was inspected by SAN-DO on June 14 – 23, 2011 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug product testing operations. The CBI, SVS, and TRP profiles were updated and are acceptable.

Manufacturing Location: Singapore

Firm Name: Roche Singapore Technical Operations Pte. Ltd.

Address: 10 Science Park Road, Singapore, 637394

FEI: 3007164129

Short summary of manufacturing activities performed: Virus and Mycoplasma Testing

This site was inspected by IOG on April 26 – May 3, 2012 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug product testing operations. The TRP profile was updated and is acceptable.

Manufacturing Location: Germany

Firm Name: Roche Pharma AG

Address: Emil-Barrello-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

FEI: 3002807206

Short summary of manufacturing activities performed: Release Testing for Drug Product
(with the exception of sterility and endotoxin)

This site was inspected by IOG on September 19 – 21, 2011 and classified VAI. This was a PLI and a routine GMP surveillance inspection covering Actemra drug product testing operations. The CTL profile was updated and is acceptable.

OVERALL RECOMMENDATION

There are no ongoing or pending compliance actions that prevent approval of this supplement.

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/s/

RANJANI PRABHAKARA
04/19/2013

Bowen, Philantha

From: Bowen, Philantha
Sent: Wednesday, April 17, 2013 2:12 PM
To: 'Stuart Heminway'
Subject: sBLA 125276/64 (Actemra) - FDA Request for Labeling Revisions

Importance: High

Hello Stuart,

Reference is made to the FDA labeling information requests dated April 16 and 17, 2013.

The following labeling request pertains to the HIGHLIGHTS Section of the package insert. Deletions are in strikethrough and insertions are noted in red.

----- INDICATIONS AND USAGE-----

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

Please note that we may have additional requests as we continue our review of the labeling. In your response to the aforementioned labeling requests, include your response to this request.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
☎ 301-796-9718
✉ philantha.bowen@fda.hhs.gov

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender immediately by e-mail or phone.

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/s/

PHILANTHA M BOWEN
04/18/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

ELECTRONIC TRANSMITTAL SHEET

DATE: April 17, 2013

To: Stuart Heminway, Program Director Regulatory Affairs	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Genentech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Email: Heminway.stuart@gene.com	
Phone number: 650-467-8460	Phone number: 301-796-2466

Subject: BLA 125276/64 **Re:** FDA Labeling Recommendations/Revisions #3

Total no. of pages including cover: 3

Comments: Please Acknowledge Receipt: **TIME SENSITIVE**

Document to be mailed: YES x NO

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BLA 125276/64
Actemra (tocilizumab)
Genentech

Dear Mr. Heminway:

Your submission dated April 3, 2013, to sBLA 125276/64 containing revised labeling is currently under review and we have a request for labeling revisions. In our request below, the FDA-proposed insertions are underlined and deletions are in strike-out for the package insert. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label.

Package Insert

DOSAGE AND ADMINISTRATION – *Section 2.4 General Considerations for Administration*

1. Step 1. Withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA injection required for the patient's dose from the infusion bag or bottle.
2. Step 2, *revise the statement* “ Slowly add ACTEMRA for intravenous infusion from each vial into the infusion bag or bottle” *to the following:*

Deleted: solution

“Slowly add the volume of ACTEMRA injection required for the patient's dose into the infusion bag or bottle”.

We refer to our labeling information request dated April 16, 2013. Submit revised labeling incorporating requests listed above, as well as the FDA labeling recommendations provided in our April 16, 2013, labeling information request. Provide a clean copy and a tracked-change version of the Package Insert and Medication Guide to the sBLA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

BLA 125276/64
Actemra (tocilizumab)
Genentech

Drafted: Bowen/4-17-13

Clearance: Jafari/4-17-13
Yim/4-17-13
Nikolov/4-17-13

Finalized: Bowen/4-17-13

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/s/

PHILANTHA M BOWEN
04/17/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC TRANSMITTAL SHEET

DATE: April 16, 2013

To: Stuart Heminway, Program Director Regulatory Affairs	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Genentech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Email: Heminway.stuart@gene.com	
Phone number: 650-467-8460	Phone number: 301-796-2466
Subject: BLA 125276/64 Re: FDA Labeling Recommendations/Revisions #2	

Total no. of pages including cover: 36

Comments: Please Acknowledge Receipt: **TIME SENSITIVE**

Document to be mailed: YES NO

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BLA 125276/64
Actemra (tocilizumab)
Genentech

Dear Mr. Heminway:

Your submission dated April 3, 2013, to sBLA 125276/64 containing revised labeling is currently under review and we have a request for labeling revisions. The enclosed label contains FDA comments and/or request as to some of the changes made in the package insert. The FDA-proposed insertions are underlined and deletions are in strike-out. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating requests/changes shown in the attached marked up label for the Package Insert. Provide a clean copy and a tracked-change version of the Package Insert and Medication Guide by COB Wednesday, April 17, 2013, to the sBLA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Following this page 33 pages have been withheld in full due to draft labeling (b) (4)

BLA 125276/64
Actemra (tocilizumab)
Genentech

Drafted: Bowen/4-15-43

Clearance: Jafari/4-15-13
Yim/4-15-13
Nikolov/4-16-13
Doddapaneni/4-15-13

Finalized: Bowen/4-16-13

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/s/

PHILANTHA M BOWEN
04/16/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC TRANSMITTAL SHEET

DATE: April 9, 2013

To: Stuart Heminway, Program Director Regulatory Affairs	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Genentech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Email: Heminway.stuart@gene.com	
Phone number: 650-467-8460	Phone number: 301-796-2466
Subject: BLA 125276/64 Re: Post-Marketing Requirement Information Request	

Total no. of pages including cover: 3

Comments: Please Acknowledge Receipt: **TIME SENSITIVE**

Document to be mailed: YES NO

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BLA 125276/64
Actemra (tocilizumab)
Genentech

Dear Mr. Heminway:

Your submission dated June 28, 2012, to sBLA 125276/64, is currently under review. We have the following comments or requests for information:

We have identified the following post-marketing requirement (PMR) for Actemra (tocilizumab), provided that the supplemental application BLA 125276/64 is approved. Submit a correspondence with your agreement to conduct the PMR and include the following milestones: a) final protocol submission date, b) study completion date, and c) final report submission date.

- A long-term safety study in X pediatric patients 2-17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of pediatric pJIA patients. Patients should be followed for X years.

Submit a draft proposal to address this PMR. Your proposal should include a rationale for the proposed duration and number of patients enrolled. Submit your agreement and response officially to the sBLA by 12NN EST Monday, April 15, 2013. In addition, please forward a courtesy copy to me via email.

If you have any questions, please contact Philantha Bowen, Regulatory Project Manager, at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

BLA 125276/64
Actemra (tocilizumab)
Genentech

Drafted: Nikolov/3-8-13
Edited: Yim/3-8-13
Seymour/3-8-13

Clearance: Jafari/3-9-13

Finalized: Bowen/3-9-13

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/s/

PHILANTHA M BOWEN
04/09/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

ELECTRONIC TRANSMITTAL SHEET

DATE: March 28, 2013

To: Stuart Heminway, Program Director Regulatory Affairs	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Genentech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Email: Heminway.stuart@gene.com	
Phone number: 650-467-8460	Phone number: 301-796-2466
Subject: BLA 125276/64 Re: FDA Labeling Recommendations/Revisions	

Total no. of pages including cover: 36

Comments: Please Acknowledge Receipt: **TIME SENSITIVE**

Document to be mailed: YES NO

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BLA 125276/64
Actemra (tocilizumab)
Genentech

Dear Mr. Heminway:

Your submission dated October 24, 2012, to BLA 125276/64 is currently under review and we have a request for labeling revisions. The enclosed label contains FDA comments and/or request as to some of the changes made in the package insert. The FDA-proposed insertions are underlined and deletions are in strike-out. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating requests/changes shown in the attached marked up label for the Package Insert. Provide a clean copy and a tracked-change version of the Package Insert and Medication Guide by Wednesday, April 3, 2013, to the BLA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Following this page 33 pages have been withheld in full due to draft labeling (b) (4)

BLA 125276/64
Actemra (tocilizumab)
Genentech

Drafted: Bowen/3-27-13

Clearance: Jafari/3-27-13
Yim/3-27-13
Doddapaneni/3-27-13

Finalized: Bowen/3-28-13

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/s/

PHILANTHA M BOWEN
03/28/2013

Final Request

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

Division Goal Date: April 22, 2013
PDUFA Action Date: April 29, 2013

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125276/64
Product(s): Actemra ® (tocilizumab)

Short summary of application: *This is an efficacy supplement for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. This sBLA submission also address the PREA PMR in the original approval letter dated January 8, 2010.*

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Chugai Pharma Mfg. Co.
Address: 16-3 Klyohara Kogydanchi, Utsunomiya-city Tochigi, 321-3231,
Japan
FEI: 3006942691
Short summary of manufacturing activities performed: Drug substance and drug

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

product manufacturing

Manufacturing Location:

Firm Name: **Genentech**

Address: **One Antibody Way, Oceanside, CA 92056-5802**

FEI: **3006129086**

Short summary of manufacturing activities performed: **Drug Substance Manufacturing and Release Testing**

Manufacturing Location:

Firm Name: **Genentech**

Address: **1 DNA Way, South San Francisco, CA 94080-4990**

FEI: **2917923**

Short summary of manufacturing activities performed: **Virus and Mycoplasma Testing**

Manufacturing Location:

Firm Name: **Roche Singapore Technical Operations Pte. Ltd.**

Address: **10 Science Park Road, Singapore, 637394**

FEI: **3007164129**

Short summary of manufacturing activities performed: **Virus and Mycoplasma Testing**

Manufacturing Location:

Firm Name: **Roche Pharma AG**

Address: **Emil-Barrello-Strasse 1
D-79639 Grenzach-Wyhlen
Germany**

FEI: **3002807206**

Short summary of manufacturing activities performed: **Release Testing for Drug Product (with the exception of sterility and endotoxin)**

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/s/

PHILANTHA M BOWEN
03/26/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC TRANSMITTAL SHEET

DATE: January 15, 2013

To: Stuart Heminway, Program Director Regulatory Affairs	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Genentech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: Heminway.stuart@gene.com	Fax number: 301-796-9728
Phone number: 650-467-8460	Phone number: 301-796-2466
Subject: sBLA 125276/64 Re: Clinical Pharmacology Request	

Total no. of pages including cover: 3

Comments: Please Acknowledge Receipt: **TIME SENSITIVE**

Document to be mailed: YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

sBLA 125276/64
ACTEMRA® (tocilizumab)
Genentech, Inc.

Dear Mr. Heminway:

Your submission dated June 28, 2012, to sBLA 125276/64 is currently under review. We have the following request for information:

Submit the dataset and code used to calculate mean(+SD) Cmin, Cmax, AUC4weeks and accumulation ratios of tocilizumab as proposed in the label.

Submit the requested information by Friday, January 18, 2013, to the sBLA. Forward a courtesy copy via email to philantha.bowen@fda.hhs.gov.

If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted	Bowen 1-15-13
Clearance	Jafari 1-15-13 Bhattaram 1-15-13 Doddapaneni 1-15-13
Finalized	Bowen 1-15-13

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/s/

PHILANTHA M BOWEN
01/15/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: April 29, 2013

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125276/64
Product(s): Actemra ® (tocilizumab)

Short summary of application: *This is an efficacy supplement for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. This sBLA submission also address the PREA PMR in the original approval letter dated January 8, 2010.*

FACILITY INFORMATION

Manufacturing Location:
Firm Name: **Chugai Pharma Mfg. Co.**
Address: **16-3 Klyohara Kogydanchi, Utsunomiya-city Tochigi, 321-3231,
Japan**
FEI: **3006942691**
Short summary of manufacturing activities performed: **Drug substance and drug product manufacturing**

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

Inspected by IOG from 1/24/11-2/1/11 and classified VAI. This inspection provided coverage for Actemra manufacturing operations and found the CBI and SVS profiles updated and acceptable.

Manufacturing Location:

Firm Name: **Genentech**

Address: **One Antibody Way, Oceanside, CA 92056-5802**

FEI: **3006129086**

Short summary of manufacturing activities performed: **Drug Substance Manufacturing and Release Testing**

Inspected by LOS-DO from 9/2/10-9/15/10 and classified NAI. This CGMP inspection found the BTP and CTX profiles updated and acceptable.

Manufacturing Location:

Firm Name: **Genentech**

Address: **1 DNA Way, South San Francisco, CA 94080-4990**

FEI: **2917923**

Short summary of manufacturing activities performed: **Virus and Mycoplasma Testing**

Inspected by SAN-DO from 9/2/11-9/26/11 and classified VAI. This biotech CGMP inspection covered biologic manufacturing operations and found the CBI profile updated and acceptable.

Manufacturing Location:

Firm Name: **Roche Singapore Technical Operations Pte. Ltd.**

Address: **10 Science Park Road, Singapore, 637394**

FEI: **3007164129**

Short summary of manufacturing activities performed: **Virus and Mycoplasma Testing**

Inspected by CDER-DMPQ from 8/16/10-8/24/10 and classified VAI. This was a comprehensive pre-approval inspection for Bevacizumab drug substance manufacturing operations, however testing operations were covered. The TRP profile was updated and found acceptable.

Manufacturing Location:

Firm Name: **Roche Pharma AG**

Address: **Emil-Barrello-Strasse 1
D-79639 Grenzach-Wyhlen
Germany**

FEI: **3002807206**

Short summary of manufacturing activities performed: **Release Testing for Drug Product (with the exception of sterility and endotoxin)**

Inspected by IOG from 9/19/11-9/21/11 and classified VAI. This inspection covered testing operations in support Actemra and found the CTL profile updated and acceptable.

OVERALL RECOMMENDATION:

There are no pending or ongoing compliance actions that prevent approval of this supplement. Please resubmit this TB-EER 30 days before the planned action date for an updated compliance evaluation.

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/s/

MAHESH R RAMANADHAM
10/04/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: April 29, 2013

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125276/64
Product(s): Actemra ® (tocilizumab)

Short summary of application: *This is an efficacy supplement for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. This sBLA submission also address the PREA PMR in the original approval letter dated January 8, 2010.*

FACILITY INFORMATION

Manufacturing Location:
Firm Name: **Chugai Pharma Mfg. Co.**
Address: **16-3 Klyohara Kogydanchi, Utsunomiya-city Tochigi, 321-3231,
Japan**
FEI: **3006942691**
Short summary of manufacturing activities performed: **Drug substance and drug product manufacturing**

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

Manufacturing Location:

Firm Name: **Genentech**

Address: **One Antibody Way, Oceanside, CA 92056-5802**

FEI: **3006129086**

Short summary of manufacturing activities performed: **Drug Substance Manufacturing and Release Testing**

Manufacturing Location:

Firm Name: **Genentech**

Address: **1 DNA Way, South San Francisco, CA 94080-4990**

FEI: **2917923**

Short summary of manufacturing activities performed: **Virus and Mycoplasma Testing**

Manufacturing Location:

Firm Name: **Roche Singapore Technical Operations Pte. Ltd.**

Address: **10 Science Park Road, Singapore, 637394**

FEI: **3007164129**

Short summary of manufacturing activities performed: **Virus and Mycoplasma Testing**

Manufacturing Location:

Firm Name: **Roche Pharma AG**

Address: **Emil-Barrello-Strasse 1
D-79639 Grenzach-Wyhlen
Germany**

FEI: **3002806559**

Short summary of manufacturing activities performed: **Release Testing for Drug Product (with the exception of sterility and endotoxin)**

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/s/

PHILANTHA M BOWEN
09/28/2012



BLA 125276/64

FILING COMMUNICATION

Hoffman-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110

Attention: Kristine L. Ogozalek, Program Director
Regulatory Program Management

Dear Ms. Ogozalek:

Please refer to your Supplemental Biologics License Application (sBLA) dated June 28, 2012, received June 29, 2012, submitted under section 351 of the Public Health Service Act for Actemra (tocilizumab).

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is April 29, 2013.

We are reviewing your supplemental application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post-marketing commitment requests by March 29, 2013.

We request that you submit the following information:

- Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. If submitting as a PDF document, include mapping in both directions (verbatim -> preferred and preferred -> verbatim).

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights Section: Revise the Patient Counseling Information Statement as shown:
See 17 for PATIENT COUNSELING INFORMATION and (b) (4)
Medication Guide
2. Full Prescribing Information Section 17: Patient Counseling Information, *add the wording as follows directly under the section heading:*

See FDA-approved patient labeling (Medication Guide)

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by September 12, 2012. The resubmitted labeling will be used for further labeling discussions. Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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.

We note that you have submitted pediatric studies with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application. We reference the partial waiver granted on January 8, 2010, for the pediatric study requirement for patients with juvenile idiopathic arthritis polyarticular subtype 0 to < 2 years of age.

If you have any questions, call Philantha Bowen, Senior Regulatory Project Management Officer, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

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

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/s/

LYDIA I GILBERT MCCLAIN
08/28/2012
Deputy Division Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Philantha Bowen, RPM ODEII/DPARP 301-796-2466		
DATE August 9, 2012	IND NO.	BLA NO. 125276/64	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT June 28, 2012
NAME OF DRUG Actemra (tocilizumab)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Monoclonal Antibody	DESIRED COMPLETION DATE March 15, 2013
NAME OF FIRM: Genentech, A Member of the Roche Group				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input checked="" type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: We are requesting your review and evaluation of the Risk Management Plan (REMS and REMS Supporting Document) proposed in this efficacy supplement dated June 28, 2012. The link to the submission is below. The planned meetings are: Mid-Cycle: 11/27/12 Labeling: 2/27/13 Wrap Up: 3/19/13 PDUFA Date: April 29, 2013 Link to submission (6/28/12) http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681068faf				
SIGNATURE OF REQUESTER <i>See appended electronic signature</i>		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

PHILANTHA M BOWEN
08/09/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION			
TO: CDER-DMPP-PatientLabelingTeam			FROM: (Name/Title, Office/Division/Phone number of requestor) Philantha Bowen, RPM ODEII/DPARP 6-2466		
REQUEST DATE: August 9, 2012		NDA/BLA NO.: 125276/64	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)		
NAME OF DRUG: Actemra (tocilizumab)	PRIORITY CONSIDERATION:		CLASSIFICATION OF DRUG: Monoclonal antibody	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) March 15, 2013	
SPONSOR: Hoffman LaRoche			PDUFA Date: April 29, 2013		
TYPE OF LABEL TO REVIEW					
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION	
EDR link to submission:					
Link to submission (6/28/12) < http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681068faf >					
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.					
COMMENTS/SPECIAL INSTRUCTIONS:					
Filing/Planning Meeting: 8/6/12					
Mid-Cycle Meeting: 11/27/12					
Labeling Meetings: 2/27/13					
Wrap-Up Meeting: 3/19/13					
SIGNATURE OF REQUESTER <i>See appended electronic signature</i>					
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS		

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/s/

PHILANTHA M BOWEN
08/09/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Philantha Bowen, RPM ODEII/DPARP 796-2466	
REQUEST DATE August 9, 2012	IND NO.	NDA/BLA NO 125276/64	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Actemra (tocilizumab)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Monoclonal Antibody	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) March 15, 2013
NAME OF FIRM: Hoffman LaRoche		PDUFA Date: April 29, 2013	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
---	--	---

EDR link to submission:

Link to submission (6/28/12)
<<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681068faf>>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: 11/27/12
Labeling Meetings: 2/27/13
Wrap-Up Meeting: 3/19/13

SIGNATURE OF REQUESTER
See appended electronic signature

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
 eMAIL
 DARRTs

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/s/

PHILANTHA M BOWEN
08/09/2012



BLA 125276/64

**PRIOR APPROVAL SUPPLEMENT -
ACKNOWLEDGEMENT**

Hoffman-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110

Attention: Kristine L. Ogozalek, Program Director
Regulatory Program Management

Dear Ms. Ogozalek:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351 of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 64
PRODUCT NAME: Actemra (tocilizumab)
DATE OF SUBMISSION: June 28, 2012
DATE OF RECEIPT: June 29, 2012
US LICENSE NUMBER: 1048

This supplemental application proposes the following indication: the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 28, 2012, in accordance with 21 CFR 601.2(a).

If the application is filed, the user fee goal date will be April 29, 2013.

CONTENT OF LABELING

If you have not already done so, promptly submit 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha M. Bowen, M.P.H., RN
Senior Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PHILANTHA M BOWEN
07/30/2012

Debarment Certification

DEBARMENT CERTIFICATION

Genentech Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
Genentech, Inc.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 11972

**MEETING REQUEST -
Written Responses**

Hoffman-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110

Attention: Kristine L. Ogozalek, Associate Director
Regulatory Affairs

Dear Ms. Ogozalek:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tocilizumab.

We also refer to our February 10, 2012, communication notifying you that we would provide a written response to the questions in your January 25, 2012, meeting request following receipt of your background materials. We received your background materials on March 09, 2012.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, call me, at (301) 796-3367.

Sincerely,

{See appended electronic signature page}

Leila P. Hann
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure :
Written Responses

QUESTIONS AND RESPONSES

Question 1

Roche intends to file the data from study WA19977 to support the submission of a sBLA for Tocilizumab for the following indication:

Actemra is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in (b) (4) patients 2 years of age and older.

Does the Agency agree that the efficacy and safety data support the filing?

FDA Response:

The safety and efficacy data summarized in the briefing package appear to be adequate to support filing of an application for polyarticular juvenile idiopathic arthritis (pJIA). However, determination of the approvability of the application will be contingent upon review of the sBLA.

Question 2

Given the available efficacy and safety data presented here, Roche believes that the recommended dose of Tocilizumab for pJIA patients should be 8mg/kg in pediatric patients weighing ≥ 30 kg and 10mg/kg for pediatric patients weight < 30 kg every 4 weeks.

Does the Agency agree with this dose regimen recommendation based on available data?

FDA Response:

Your dose regimen may be reasonable; however, selection of the dose regimen will be determined based on review of the sBLA.

Question 3

Secondary endpoints in the Roche study (WA1997) include an assessment of the effect of tocilizumab on achieving JIA ACR30/50/70 responses at week 16 and maintaining an ACR response to week 40. (b) (4)

Therefore, Roche proposes to include this information in the label.

Does the Agency agree?

FDA Response:

It may be reasonable to include (b) (4) you propose depending on demonstration of substantial evidence of efficacy with adequate control of the Type I error rate. However, the content of the label will be determined based on review of the sBLA.

Question 4

Does the Agency agree with the Risk Evaluation and Mitigation Strategy (REMS) plan, specifically:

- a) *The Sponsor believes the identified risks of tocilizumab in the pJIA patient population are consistent with that seen in adult RA and can be managed via the existing Actemra REMS. Currently no data has been seen in this population that would warrant additional REMS elements (e.g. ETASU) to manage risk. The Sponsor intends to modify the REMS proposal in the sBLA to include the new pJIA indication. Does the Agency agree?*
- b) *Roche seeks guidance from the Agency on the assessment of the REMS for this efficacy supplement for the new indication of pJIA. Given that the ACTEMRA REMS has had a full assessment in the previous 18 months (18-month Assessment submission date of July 7, 2011), the Sponsor proposes not to include a full REMS assessment within this filing, but instead referring to the 18-month Assessment and including an update on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. Does the Agency agree with this approach?*

FDA Response:

4a. Your plan seems generally reasonable depending on review of the data.

4b. Your plan seems generally reasonable depending on review of the data.

Question 5

Does the Agency agree with the planned content and format of Module 2, particularly the clinical pharmacology, efficacy and safety summaries, and that the data from studies conducted by Chugai and Roche do not need to be pooled?

FDA Response:

We do not agree. We will assess the safety of your product for the proposed indication and population relative to the overall safety of tocilizumab, including safety in the adult RA population. Therefore, in Module 2, provide a summary of the clinical safety to compare safety and efficacy in the pediatric population relative to the overall safety of the drug. Efficacy data from the adult RA population, however, should not be included in this sBLA.

We agree that the data from studies conducted by Chugai and Roche do not need to be pooled.

Question 6

Does the Agency agree with the planned content and format of Module 5, specifically:

- a) *The Sponsor proposes to include datasets, analysis datasets and non-executable programs for WA19977, however not for the Japanese studies MRA3181 and MRA319JP, as these studies are supportive. Does the Agency agree?*
- b) *The Sponsor proposes to provide WA19977 CRFs for deaths and patient withdrawals due to an AE and Patient data profiles will be provided for deaths and patient withdrawals due to AEs in lieu of CRFs for MRA318JP and MRA319JP.*

FDA Response:

6a. We agree that datasets for Japanese studies MRA3181 and MRA319JP do not need to be included in Module 5 provided that data from these trials will not be used to support the efficacy of tocilizumab for pJIA.

6b. Provided the patient data profiles for trials MRA318JP and MRA319JP contain all the data from the CRFs, your plan is acceptable.

Question 7

The Sponsor intends to provide a 4 Month Safety Update with the safety from WA19977 and post-marketing data as described below, with a clinical cut off of May 3, 2012. Does the Agency agree with the content of this proposal?

FDA Response:

Your plan seems generally reasonable depending on review of the data and the date of your sBLA submission.

Question 8

In the cover letter, Roche plans to reference the original Actemra BLA submission dated December 20, 2007 and the BLA approval letter on January 8, 2010, which waived the pediatric study requirement for ages 0 to <2 years. The request for a waiver for children with pJIA less than 2 years of age will not be reiterated. Does the Agency agree?

FDA Response:

We agree. Trial WA19977, which forms the basis of your proposed sBLA submission, was a post-marketing requirement under PREA. As such, designate your submission "REQUIRED PEDIATRIC ASSESSMENT."

Question 9

Roche intends to provide financial disclosure certification for study WA19977. Roche does not intend to submit financial disclosure information for the Chugai Studies (MRA318 and MRA319) as these were not collected and these studies do not fit the definition of 'covered study'. Does the agency agree?

FDA Response:

We agree.

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/s/

LEILA P HANN
05/01/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

IND 11,972

Hoffmann-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110

Attention: Matthew Lamb, Pharm.D
Director, Global Regulatory Affairs

Dear Dr. Lamb:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tocilizumab for the treatment of adult onset rheumatoid arthritis.

We also refer to the teleconference between representatives of your firm and the FDA on March 5, 2009. The purpose of the meeting was to discuss your plans to address the stratification strategy, statistical analyses, and patient population in juvenile idiopathic arthritis study to ensure agreement on the Special Protocol Assessment (SPA).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-796-2254.

Sincerely,

{See appended electronic signature page}

Sharon Turner-Rinehardt
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEETING MINUTES

Meeting Date: March 5, 2009
Meeting Type: Teleconference
IND/Name: 11,972/Tocilizumab
Indication: Juvenile Idiopathic Arthritis
Sponsor: Hoffmann-La Roche
Type of Meeting: Type A, SPA
Meeting Chair: Sarah Okada, M.D., Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170
Minutes Recorder: Sharon Turner-Rinehardt, RPM



BACKGROUND: The Sponsor submitted a Special Protocol Assessment (SPA) dated November 17, 2008, which was reviewed by the Division and a non-agreement was issued on January 16, 2009, for the SPA. The Sponsor requested a meeting to address some of the deficiencies cited in the letter such as the stratification strategy, statistical analyses, and patient population in juvenile idiopathic arthritis study to ensure agreement of a SPA.

Roche Attendees	
Name	Title
Matthew Lamb, PharmD	Global Regulatory Leader, Regulatory Affairs
Kristine Ogozalek	US Regulatory Affairs
Joel Krasnow, MD	Clinical Science Leader
(b) (6) MD	Clinical Science
(b) (6)	Clinical Science
(b) (6)	Statistician
Liz Thompson	Statistical Team Leader
Yamo Deniz, MD	Clinical Science Leader
(b) (6), MD	Drug Safety
FDA Attendees	
Name	Title
Rigoberto Roca, MD	Deputy Director
Sarah Okada, MD	Clinical Team Leader
Kathleen Coyle, MD	Medical Officer
Jonathan North, PhD	Statistical Reviewer
Dionne Price, PhD	Statistical Team Leader
Thomas Permutt, PhD	Director, Biometrics II
Sharon Turner-Rinehardt	Regulatory Health Project Manager

GENERAL DISCUSSION:

Following introductions, the meeting focused on the response to the question 5 included in the February 18, 2009, meeting package for IND 11,972. The Sponsor accepted the Division responses to questions 1, 2, 3, and 4. The questions are presented below in *italicized* text. The Division's responses, prepared prior to the meeting and sent to the Sponsor via email on March 2, 2009, are **bolded**. Discussion is presented in normal text. The meeting was conducted via teleconference.

AGENDA QUESTIONS from SPONSOR and FDA COMMENTS

Question 1. The Division raised concerns about the stratification and statistical analysis in the FDA letter received January 16, 2009. Roche proposes to stratify the randomization at Part II (week 16) by two factors instead of four, these being methotrexate use, and concurrent use of corticosteroids. This will reduce the likelihood of having insufficient patients and sparse cells following randomization at the start of part II. Prior use of biologics and rheumatoid factors have been omitted as a stratification factors

Does the Division agree that this would address their concerns regarding the impact of the sparseness on randomization and analysis?

FDA Response

Yes. By reducing the number of stratification factors to two, you have addressed our concerns.

Discussion: No discussion required for this question.

Question 2. The Division raised concerns about the handling of missing values in the FDA letter received January 16, 2009. Roche proposes that last observation carried forward (LOCF) will be used for all missing JIA ACR core set components in order to determine JIA ACR 30 flare during Part II of the study. This applies only to those component values recorded in Part II (post week 16) of the study. Part I component values will not be carried forward in determination of an endpoint specific to Part II, reflecting the study design. Last observation carried forward as an imputation technique used to compensate for missing data will be investigated as to the sensitivity of the analysis results, particularly if the number of missing results is substantial. All missing value rules and sensitivity analyses will be specified in the statistical analysis plan.

Does the Division agree that this would to address their concern regarding the handling of intermittent missing values for the ACR 30 during Part II?

FDA Response

Yes. LOCF imputation is acceptable for intermittent missing values during Part II of this study.

Discussion: No discussion required for this question.

Question 3. The Division raised concerns about multiplicity given the number of secondary endpoints included in the protocol in the FDA letter received January 16, 2009. Roche proposes that a hierarchical fixed sequence approach will be applied to secondary endpoints to control for multiplicity. The hierarchical approach controls the overall false positive error rate by stating that each hypothesis test in the sequence must be significant for subsequent comparisons in the chain to be reported as significant. The pre-defined ordering of secondary endpoints will be specified in the statistical analysis plan, according to agreed scientific rationale.

Does the Division agree that this would address their concern for multiplicity?

FDA Response

You propose that “a hierarchical fixed sequence approach will be applied to secondary endpoints to control for multiplicity,” that no hypothesis be tested unless the previous hypotheses in the sequence are rejected, and that the sequence will be pre-specified in the statistical analysis plan.

Using a fixed sequence of endpoints is an acceptable way to address our concern for multiplicity.

Discussion: No discussion required for this question.

Question 4. Roche’s intends to enroll both polyarticular-course and extended oligoarticular patients in this trial and include them in the primary analysis. Roche maintains that the vast majority of children with persistent oligoarticular JIA are successfully managed with a combination of NSAIDs and intraarticular corticosteroid injections, with a high likelihood of remission in patients with this subtype. In addition, systemic corticosteroids, DMARDs or biologic treatments are rarely warranted in children with persistent oligoarticular JIA. Therefore, it is not Roche’s intent now or in the future to study persistent oligoarticular JIA with tocilizumab. Please confirm that this is agreeable to the Division.

FDA Response

This is agreeable to the Division.

Discussion: No discussion required for this question.

Question 5. In an effort to enhance the conduct of protocol WA19977 in the pediatric population, while maintaining timely assessment of safety parameters, Roche has reduced the quantity of blood sampling especially in the open label treatment portion, Part III.

These modifications include:

- *A reduction to an annual analysis of lipoprotein subclasses (sdLDL-C, sdLDL-apo B, Ox-LDL, HDL-SAA, HDL PPT by PEG).*
- *Chemistry will be split into two panels. Bilirubin, aminotransferases and creatinine will be sampled at every study visit, and the remainder of the chemistry labs assessed every eight weeks.*
- *CRP and ESR will be monitored as acute phase reactants. Serum Hepcidin, SAA, C3 and C4 will not be obtained.*
- *Roche believes that markers of cartilage turnover will be more informative than the bone markers. Therefore, markers of cartilage turnover will be assessed at baseline, weeks 2, 12, 16, 20, 52 and in the event of a flare.*
- *Bone markers will not be obtained.*
- *Anti-tocilizumab antibodies will be measured at baseline, during flare, at study end and on the basis of clinical events.*
- *Serum soluble IL-6 receptor and serum IL-6 will be captured in part I, and II but not in part III.*
- *Cytokine panels (sIL-1Ra, IL-1 β , TNF- α , IL-17, IL-18, sgp130R, SC5b-9), other than IL-6 and soluble IL-6 receptor, will not be obtained.*

In addition, the Childhood Assessment Questionnaire (CHQ) will be eliminated from WA19977. The Childhood Health Assessment Questionnaire (CHAQ), a required JIA core outcome variable, has been retained.

The revised protocol will incorporate these changes and in the forthcoming SPA the details of these scheduling changes will be clearly identified.

Does the division agree that reduction in frequency or in some cases elimination of these lab assessments is acceptable?

FDA Response

Yes, the proposed revision of lab assessments is acceptable.

Discussion: The Sponsor asked whether it was acceptable to collect genomic biomarker samples in the SPA protocol. The Division stated that as this is acceptable as long as the total amount of blood collected does not exceed safe levels.

Additional Discussion:

The Sponsor wanted clarification on the next steps regarding the SPA and whether this meeting constituted an agreement of the SPA. The Division stated that this meeting was not a SPA agreement, and that the Sponsor must submit the revised protocol for the SPA which will undergo the normal 45-day review period and culminate in a formal notification.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 11972

HOFFMANN-LA ROCHE
INC

Humanized Monoclonal Antibody (MRA) to
Interleukin-6 Receptor

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/s/

SHARON M TURNER RINEHARDT
04/03/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 11972

Hoffman-La Roche Inc.
340 Nutley Street
Nutley, NJ 07110

Attention: Matthew W. Lamb, PharmD
Director, Global Regulatory Affairs

Dear Dr. Lamb:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tocilizumab (MRA, RO4877533).

We also refer to the meeting between representatives of your firm and FDA on March 20, 2007. The purpose of the meeting was to discuss the Phase 3 development of tocilizumab in pediatric patients, including the treatment of systemic Juvenile Idiopathic Arthritis (sJIA), and polyarticular-course Juvenile Idiopathic Arthritis (pJIA) patients.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE

SPONSOR MEETING AGENDA

MEETING DATE: March 20, 2007
TIME: 3 PM
LOCATION: 10903 NH Ave; Silver Spring, MD 20903; Bldg 22; Conf Rm 1313
APPLICATION: IND 11972
APPLICATION STATUS: Active
PRODUCT: tocilizumab
INDICATION: (for this meeting) systemic-onset Juvenile Idiopathic Arthritis (sJIA)
SPONSOR: Hoffman La-Roche Inc.
TYPE OF MEETING: EOP2 for above indication
MEETING CHAIR: Jeff Siegel, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
MEETING RECORDER: Lisa Basham, Regulatory Project Manager

FDA	Title	Signature
Bob Rappaport, MD	Division Director	
Rigoberto Roca, MD	Deputy Division Director	
Jeffrey Siegel, MD	Clinical Team Leader, Rheumatology	
Sarah Okada, MD	Acting Clinical Team Leader, Rheumatology	
Dionne Price, PhD	Team Leader, Statistics	
Sarah Cochran, MD	Clinical Reviewer	
Sally Choe, PhD	Clinical Pharmacology Reviewer	
Joan Buenconsejo, PhD	Statistics Reviewer	
Gerald Feldman, PhD	Senior Investigator, Laboratory of Molecular and Developmental Immunology	
Carolyn Yancey, MD	Clinical Reviewer	
Eric Brodsky, MD	Clinical Reviewer	
Lisa Basham, MS	Regulatory Project Manager	
Hoffman La-Roche Inc.	Title	
Dr. Matthew Lamb	Reg Affairs, Global Regulatory Leader	
Ms. Robin Conrad	Reg Affairs, Senior Director	
Ms. Janet Czachura	Reg Affairs (US), Senior Program Manager	
Dr. Thasia Woodworth	Global Clinical Science Leader	
Dr. Randall Stevens	Clinical Science, Vice President	
Dr. Warren Greth	Clinical Science, Associate Clinical Director	
Dr. Don MacLean	Global Lifescience Team Leader	
Dr. (b) (6)	Clinical Pharmacologist	
Dr. Nicolas Frey	Senior Pharmacometrician	
Dr. (b) (6)	Biostatistician	
Dr. (b) (6)	Chugai Pharmaceuticals, Clinical Development	

MEETING MINUTES

Following introductions and opening remarks, the discussion moved to the sponsor's questions and to the Agency responses provided prior to the meeting.

Note: The questions included in the meeting package are shown below in italicized text. Agency responses/comments, forwarded to the sponsor prior to the meeting, are shown below in bolded text. Discussion during the meeting is presented in normal text. Prior to the meeting, the sponsor informed Lisa Basham that they wish to concentrate discussion on the Agency's responses to questions 2, 5, 9, and 10.

Clinical Development in systemic Juvenile Idiopathic Arthritis (sJIA)

Question 1: The results of the tocilizumab sJIA development program conducted by Chugai Pharmaceuticals in Europe & Japan demonstrate control of the signs and symptoms of sJIA with an acceptable safety profile and provide a basis to initiate a Phase 3 study in patients with sJIA. Does the Agency agree?

FDA Response:

The experience with tocilizumab in the treatment of sJIA consists of two open-label studies, MRA011JP and LRO320, and their long-term, open-label extensions, and a single, controlled trial of randomized withdrawal design in 56 patients, MRA316JP. The evidence of activity and the safety profile noted in your open-label studies appears to be supported by preliminary results from MRA316JP, provided in the briefing package. These data suggest that JIA30/50/70 responses are attained and maintained in 75-80% of patients on tocilizumab compared to patients randomized to placebo, of whom only 13-17% maintained these responses. The safety profile in this trial suggests it is similar to that observed in adult RA trials, with the most common AEs being upper respiratory infections, and mild to moderate increases in liver enzymes and lipid parameters. These data suggest a sufficient basis exists to initiate a Phase 3 study in sJIA patients.

Discussion: No discussion necessary.

Question 2: The proposed design of the Phase 3 sJIA study is a multi-center, randomized, double-blind, placebo-controlled, parallel group study, with an open-label extension. Children with active sJIA aged 2 to 17 years who have an established diagnosis of sJIA for at least 6 months and an inadequate response to NSAIDs/ corticosteroids will be enrolled. The primary endpoint is a JIA30 response, assessed at week 12. All patients who qualify for escape will be considered non-responders and offered an option to enter the open-label extension. The primary efficacy analysis at week 12 is a non-responder analysis. Does the agency agree with the overall design of this Phase 3 study?

FDA Response:

The overall design of your proposed sJIA study appears to be acceptable. However, you have proposed a secondary endpoint of the proportion of patients on oral steroids at Week 6 with JIA70 who reduced steroid dose by at least 20%. If a patient is on high dose corticosteroids, then a 20% reduction may not be clinically meaningful, e.g. a 20% reduction from a starting dose of 60 mg would still be a high dose at 48 mg. We recommend instead that you assess the proportion of patients who are able to achieve a taper to a clinically meaningful lower dose, i.e., a dose that would be expected to be associated with a relatively lower rate of major steroid toxicities, and the proportion of patients who are able to completely taper off steroids.

Discussion: The sponsor discussed their rationale for the endpoint of 20% reduction in steroid dose during the controlled portion of the trial. They selected this endpoint to achieve a reasonable level of corticosteroid taper during this portion of the trial without interfering with the assessment of treatment efficacy. They proposed to add an endpoint to the open-label extension of the trial to assess the proportion of patients who are able to achieve a taper to a clinically meaningful lower dose, e.g., ≤ 0.2 mg/kg (maximum ≤ 10 mg) daily, with landmark analyses to be done at intervals during the open-label period. The Division acknowledged the sponsor's rationale for steroid tapering and choice of endpoint in the controlled portion of the trial, and explained that data from both portions of the trial could be used to assess the effect of treatment on ability to taper corticosteroids. Whether this information could be included in labeling will depend on the strength of the data—i.e., whether taper to clinically meaningful lower doses of steroids can be achieved and whether analyses have been pre-specified, in order to minimize bias. The sponsor asked the Division whether ≤ 0.2 mg/kg (maximum ≤ 10 mg) daily was reasonable as a choice for a clinically meaningful lower dose. The Division replied that, while this sounds reasonable, the sponsor should choose a dose after consultation with pediatric rheumatologists, and they should submit a rationale for this choice in the submission.

FDA Response to Question 2, continued:

The proportion of patients with fever of systemic JIA at baseline who are free of fever by Week 12 should be treated as an important secondary endpoint in order to demonstrate the activity of tocilizumab in the treatment of systemic inflammatory features of sJIA. To obtain an indication of "treatment of systemic JIA" you would need to show efficacy for the arthritis (as assessed based on the JIA30) and the systemic features (based on an increase in the proportion of patients free of fever). If you showed an effect only on the JIA30, you would obtain an indication for "treatment of the active arthritis associated with systemic JIA." As mentioned in the Pre-IND/Pre-Phase 3 meeting of September 21, 2004, you should also assess the response to treatment in other systemic inflammatory features such as the proportion of subjects with thrombocytosis or hepatosplenomegaly at baseline who return to normal.

Discussion: The sponsor expressed their intent to evaluate the effect of treatment on systemic features of disease, such as fever, rash, thrombocytosis, leukocytosis, serositis and hepatosplenomegaly, but that the trial would be powered to assess the primary endpoint of JIA 30 responses. Systemic endpoints would be considered secondary or exploratory, and statistical analyses may be more descriptive. However, the sponsor would like to pursue the broader indication of treatment of systemic JIA if there is sufficient evidence to support it. The Division

acknowledged that it could be difficult to have enough patients with a given systemic inflammatory feature to show statistical significance. Therefore, if the sponsor is successful in demonstrating efficacy for the primary endpoint, the totality of the data could be used to determine whether the treatment has beneficial effects in controlling systemic inflammatory features. If the data are consistent in showing a salutary effect on systemic features, even if statistical significance is not achieved for a given parameter, then this could be used to support the broader indication.

FDA Response to Question 2, continued:

We have noted that you are planning to obtain data on the effect of treatment on growth measurements. This is valuable information that would be of significant importance to clinicians treating this disease. However, in our past experience, we have observed technical difficulties that have affected the interpretability of such data. We recommend you submit a detailed proposal for how this data will be collected, in order for us to be able to provide comments that could improve the overall interpretability of these results.

Discussion: The sponsor reiterated their intent to obtain data on the effect of treatment on growth measurements, to include 1 year of growth curve data prior to study, and a plan to standardize procedures for collecting growth measurement data during the study. They asked what sorts of technical difficulties had been observed previously. The Division stated that, in fact, the technical difficulties were related to those two issues: having an adequate amount and quality of pre-study growth curve measurements for comparison, and having adequately standardized growth measurement collection during the study in order to reduce variability of the data. The sponsor stated their intention to provide a detailed proposal with the protocol for further comment. The Division asked whether effects on growth curve measurements have been noted to date. Dr. (b) (6) from Chugai Pharmaceuticals discussed the experience in the Japanese sJIA studies and noted that catch up and restoration of the growth curve toward normal had been observed within 1- 2 years in some sJIA patients in the Japanese studies.

FDA Response to Question 2, continued:

As one of the escape criteria you mention a JIA30 flare, although this was not specifically defined in the protocol synopses. We presume you mean the standard definition of a 30% (or more) worsening in 3 of 6 JIA core set response variables with improvement of 30% (or more) in no more than one of 6 response variables. We are aware of certain circumstances in which clinical investigators and their patients did not judge disease activity to be flaring despite meeting these criteria. You should consider adding minimum worsening criteria; for example, worsening of 30% or more in 3 of 6 response variables and a minimum of two active joints [Lovell et al., NEJM 2000; 342:763-9].

It would be desirable to obtain safety and efficacy information in children over the entire age range in which sJIA occurs, to include children less than 2 years of age. Therefore, we recommend you include children younger than 2 years old in the trial as well. However, these children could be excluded from the primary efficacy analysis if the JIA core set criteria would not accurately capture the treatment effect on disease activity in this age group.

Discussion: The sponsor proposed enrolling children less than 2 years of age into the study after initial safety and efficacy data had been obtained in children over 2 years of age, and in conjunction with IRB approval. They proposed to enroll a minimum of 5 children less than 2 years of age and to obtain PK data as well as safety and efficacy information. The Division concurred with this proposal.

FDA Response to Question 2, continued:
Further comments may be provided upon final review of the protocol.

Question 3: Due to concerns regarding the feasibility of maintaining the blinded assessor beyond the initial primary efficacy assessment at 12 weeks in Part 1 of the study, Roche is considering conducting unblinded assessments of joint count as part of the JIA30 core set in the Part 2 open label period (92 weeks). In addition, objective measurements (CRP, fever, hemoglobin) will be obtained throughout the open-label period which would serve as evidence of efficacy in these patients. Does the FDA agree that the JIA30 core set (including unblinded assessment of joint counts), in addition to the objective measurements stated above, would provide confirmatory evidence of efficacy in the open-label phase of the sJIA study?

FDA Response:

The primary evidence of treatment efficacy will be determined in the controlled phase of your trial. The open-label long-term extension will be important in assessing the durability of treatment effect as well as the long-term safety and tolerability of your product, but these data are not the primary evidence for efficacy. Therefore, unblinded assessment of joint counts and the other core set criteria would be acceptable in the open-label phase. However as you have noted, objective measurements of inflammation will be important to support the findings of the subjective assessments.

Discussion: No discussion necessary.

Question 4: The dose regimen of 8 mg/kg q2wk for patients \geq 30 kg, and 12 mg/kg q2wk for patients < 30 kg will be used for the planned sJIA study. Does the Agency agree with the proposed dose regimens?

FDA Response:

Based on your population PK modeling and simulation, your proposed dose regimen of 8 mg/kg q2wk for patients \geq 30 kg, and 12 mg/kg q2wk for patients < 30 kg for planned sJIA study (WA18221) seems reasonable.

In the light of observed apparent differences in PK between Japanese and Caucasian pediatric patients and nonlinear PK property, appropriateness of the proposed dosing paradigm should be assessed with pharmacokinetic, efficacy, and safety data obtained from study WA18221 and from all other available databases.

Discussion: No discussion necessary.

Question 5: The total number of patients planned for the sJIA study is 108 (tocilizumab=72: placebo=36). The study design assumes a tocilizumab JIA30 response rate of 70%, a placebo response rate of 40%, and uses a 2:1 allocation (tocilizumab to placebo) of patients to treatment groups. Patient randomization will be stratified by baseline body weight, baseline methotrexate and oral corticosteroid use and duration of disease to assure balance of treatment groups across the stratification factors. Does the Agency agree with the randomization approach and study sample size?

FDA Response:

The sample size you have proposed appears to be acceptable. In principle, stratified randomization is acceptable. However, it is not clear how many categories you propose to use in the stratification with respect to duration of disease and baseline body weight. With your proposed sample size, large number of strata may result in sparse cells or imbalance treatment assignment.

Discussion: The sponsor clarified that each of the four categories would have two strata: baseline body weight will be stratified by weight ≥ 30 kg or < 30 kg; baseline methotrexate usage or not; duration of disease ≥ 4 years or < 4 years (based on median observed duration in the Japanese trials); and corticosteroid dose > 0.3 mg/kg or ≤ 0.3 mg/kg (based on distribution of corticosteroid doses observed in the Japanese trials, with approximately 50% of the population as cut-off). Based on their statistical assessment, stratification using these categories should not result in sparsely populated cells or imbalanced treatment assignment with the proposed sample size. The Division agreed that the rationale and stratification categories proposed appear reasonable.

Question 6: The purpose of the sJIA open label extension study is to provide continued treatment for patients who respond with at least a JIA30 level improvement, and to acquire longer duration safety data. In addition, for patients who attain a JIA50 or greater level of improvement, corticosteroid tapering will be undertaken. Does the FDA agree with sJIA open label extension study plan, and the corticosteroid tapering rules outlined in the protocol?

FDA Response:

Based on the schedule of assessments submitted in your briefing package, the type and frequency of safety and efficacy assessments during the 92 weeks of your open-label extension appear to be adequate.

The planned corticosteroid tapering rules outlined in the protocol include restrictions on the magnitude and circumstances of the taper in order to achieve an overall goal of discontinuing steroids or reducing to the lowest possible steroid dose while maintaining at least a JIA50 response. These rules appear to be reasonable.

The ability to taper corticosteroids while on tocilizumab treatment is clinically important and more likely to be demonstrated over the longer treatment course planned in the open-label extension. Therefore, you should assess the proportion of patients who are able to

achieve significant corticosteroid reduction during this open-label period, in addition to the controlled period of the study. (See response to question 2).

Discussion: No discussion necessary.

Question 7: Does the FDA agree that the proposed study in sJIA, along with supporting data available from completed Chugai sJIA studies, would generate sufficient data to support filing a supplemental BLA for sJIA?

FDA Response:

You are proposing to file your supplemental BLA for sJIA with the efficacy data from all the patients (n=108, 72 on tocilizumab, 36 on placebo) who have completed the Roche core study (12 week, double-blind, parallel group), and safety data which will include 1-year safety data from the first 50 patients who have entered the open-label, long-term extension phase. You also propose to provide supportive efficacy and safety data from the Chugai pediatric sJIA program, which will include 1-year safety data in 56 sJIA patients. What you have proposed is a reasonable safety database to submit in support of a sBLA for sJIA and it would be acceptable to pool the data from Roche and Chugai sJIA studies for the safety database in the indication, which is expected to include at least 100 sJIA patients treated for one year.

Clinical Development in polyarticular-course Juvenile Idiopathic Arthritis (pJIA)

Discussion: No discussion necessary.

Question 8: Roche proposes to conduct a single Phase 3 trial in pJIA patients. The design of the pJIA study will be a multi-center, double-blind, placebo-controlled, withdrawal study with an established diagnosis of pJIA for at least 3 months. Does the agency have any comments of the design of the pJIA study?

FDA Response:

Your proposed pJIA study includes a 12 week, two-arm (4 mg/kg and 8 mg/kg tocilizumab) open-label run-in period with responders randomized (2:1, active:placebo) to stay on their assigned dose or receive placebo for a 24 week randomized withdrawal period. The proposed primary endpoint is the proportion of patients with JIA30 flare during double-blind period, pooling the flare rate in the active treatment groups for comparison with the placebo group. In general, the design of this study appears acceptable. However, a shorter randomized withdrawal period, e.g., 12 weeks, could also be acceptable if you determine that a shorter period would be sufficient to demonstrate a difference in flare rates between groups.

Certain patients with pauciarticular JIA have disease activity of sufficient duration and severity to warrant a therapy with the potential for clinical benefit but also with some risk of significant toxicity. It would be desirable to obtain safety and efficacy information in these patients as well. Therefore, we recommend you enroll a subset of pauciarticular

patients in this trial. These patients could be excluded from the primary efficacy analysis since the JIA core set criteria may not accurately capture the effect of treatment on disease activity in these patients.

See response to question 2 for comments regarding JIA30 flare criteria.

Discussion: The sponsor agreed to enroll patients with pauciarticular JIA as a subset of the pJIA study. They proposed to enroll 20 pauciarticular patients, and would pool these patients for the safety database, but would exclude them from the primary efficacy analysis, as suggested in the Division's response. Information regarding the effect of treatment on disease activity in these patients will be provided descriptively, however. The total pJIA study sample size would then include 130 polyarticular JIA patients and 20 pauciarticular JIA patients. The Division concurred with this proposal.

Question 9: Does the FDA agree that the design and size of the proposed study in pJIA patients is sufficient to support filing a supplemental BLA for pJIA?

FDA Response:

Polyarticular JIA is considered sufficiently similar to adult RA that the efficacy findings of the studies in adults may be extrapolated to support the efficacy findings in pJIA. Therefore, a single trial in pJIA, if successful, could be sufficient to support a supplemental BLA.

You have not proposed the size of the safety database to support this indication. You should propose the number of pJIA patients to be treated overall, the number to be treated for 3-6 months, and the number to be treated for 1 year, in order for us to be able to comment on the adequacy of the size of the safety database.

Based on the brief information you have submitted, we are neither clear about the purpose of the non-inferiority assessment in the open-label, run-in period, nor about your justification for the choice of delta (20%). A non-inferiority assessment of different doses will not allow for determination of dose ranging information that would be important to describe use in clinical practice. Instead, we recommend a blinded comparison of the 4- and 8-mg/kg treatment groups in order to have an idea about differences in treatment effect size between the groups. You could still pool the active treatment groups for the primary efficacy analysis.

Discussion: The sponsor wished to defer discussion regarding doses and non-inferiority assessments in the pJIA trial as they are awaiting additional information from the adult RA trials to further inform the dose selection for the pJIA trial. The sponsor clarified that the proposed safety database for the pJIA indication would include 150 patients who will have participated in the 36-week trial (≥ 6 months of treatment), 50 patients who will have been treated for 1 year, with an additional 20 patients who will have been treated for up to 3 years. The Division responded that these data will supplement the known adult RA safety data, and should be sufficient for this supplemental indication, unless safety concerns arise that would require additional data.

General Clinical Development

Question 10: Roche proposes that the pJIA study outlined in Section III, along with supportive data from the Chugai pediatric studies, would generate data to meet the PREA requirements for the 2-17 year age range related to the adult BLA. At the time of the BLA filing in adult RA, Roche plans to request a deferral for this study and a waiver for the 0-2 year age range based on the limited available patient population who would require treatment with a biologic. Does the Agency agree?

FDA Response:

Your plan to request a deferral for the pediatric studies in JIA patients aged 2-17 years and waiver for the 0-2 age range at the time of submission of your BLA in adult RA is reasonable. You should submit your rationale for the deferral and waiver requests with your BLA submission and a formal decision will be made at that time.

Discussion: The sponsor requested clarification on whether the pJIA trial, as described and clarified in the discussion of question 9, would be sufficient to fulfill PREA requirements. The Division responded that the size of the trial and proposed safety database appear to be sufficient, pending review of the data.

ACTION ITEMS:

1. The sponsor will submit the sJIA protocol in the second quarter 2007 and will request a Special Protocol Assessment (SPA).
2. The sponsor will submit the protocol for pJIA during the 2nd quarter of 2008 and plans to begin the study during the 2nd/3rd quarter of 2008.

Linked Applications

Sponsor Name

Drug Name

IND 11972

HOFFMANN-LA ROCHE
IN

Humanized Monoclonal Antibody (MRA) to
Interleukin-6 Receptor

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/s/

LISA E BASHAM
04/05/2007