PRODUCT MONOGRAPH

Pr ACTEMRA®

tocilizumab

20 mg/mL Concentrate Solution for Infusion

Professed Standard

Interleukin Receptor Inhibitor

ACTEMRA®(tocilizumab) should be prescribed by and administered under the supervision of health care professionals who are experienced in the use of biologics in the management of patients with moderate to severe rheumatoid arthritis and who have fully familiarized themselves with the efficacy and safety profile of ACTEMRA.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	20 mg/mL Concentrate Solution for Infusion	*For a complete listing see DOSAGE FORMS, COMPOSITION and PACKAGING section.*

DESCRIPTION

ACTEMRA (tocilizumab) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass with a H2L2 polypeptide structure.

INDICATIONS AND CLINICAL USE

Rheumatoid Arthritis (RA)

ACTEMRA (tocilizumab) is indicated for:

- reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs) and/or tumour necrosis factor (TNF) antagonists. ACTEMRA in combination with methotrexate has been shown to reduce the rate of progression of radiographic joint damage at Week 52.

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

ACTEMRA is indicated for the treatment of signs and symptoms of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have responded inadequately to previous therapy with DMARDs and systemic corticosteroids.

Systemic Juvenile Idiopathic Arthritis (sJIA)

ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with one or more non steroidal anti-inflammatory drugs and systemic corticosteroids.

CONTRAINDICATIONS

ACTEMRA (tocilizumab) should not be administered to patients with known hypersensitivity to tocilizumab or any of its components. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

Patients with active infections (see also WARNINGS AND PRECAUTIONS, Serious Infections).

WARNINGS AND PRECAUTIONS

WARNING: RISK OF SERIOUS INFECTIONS

Serious infections including sepsis, tuberculosis (TB), invasive fungal, and other opportunistic infections have been observed with the use of biologics agents, including ACTEMRA. Hospitalization or fatal outcomes associated with infections have been reported.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for both active and latent tuberculosis before ACTEMRA use and during therapy. Treatment should be completed 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.**

Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids, that, in addition to their rheumatoid arthritis could predispose them to infections.

Before starting treatment with ACTEMRA, all patients should be evaluated for both active and latent tuberculosis.

Treatment with ACTEMRA should not be initiated in patients with active infections including chronic or localized infections.

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

ALL INDICATIONS

1. Serious Infections

Concurrent therapy with ACTEMRA and another biologic agent is not recommended. When transitioning from another biologic therapy to ACTEMRA, patients should be monitored for signs of infection. In the clinical trials in adults, a higher incidence of infections was observed in patients previously exposed to a TNF inhibitor.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic infections have been observed 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. Opportunistic infections including tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidiomycosis, listeriosis). Patients have presented with disseminated rather than localized disease. Rheumatoid arthritis itself as well as concomitant immunosuppressants treatment such as methotrexate or corticosteroids are additional risk factors for serious infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA.

Patients with sJIA also reported the following serious infections: varicella and mycoplasmal pneumonia.

Treatment with ACTEMRA should not be initiated in patients with active infections including chronic or localized infections. Administration of ACTEMRA should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis, until the infection is controlled (see DOSAGE AND ADMINISTRATION: Dosing Considerations).

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.

Vigilance for the timely detection of serious infection is recommended for patients receiving treatment with ACTEMRA for rheumatoid arthritis, pJIA or sJIA, as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reactants. 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.

Patients and parents/guardians of minors with pJIA or sJIA should be instructed to contact a physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

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

Patients with latent or active tuberculosis should complete treatment with standard anti-mycobacterial therapy before 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 and/or ACTEMRA 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 tuberculosis infection prior to initiating therapy.

Viral Reactivation
Treatment with TNF inhibitors has been associated with reactivation of hepatitis B and C and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. Therefore screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ACTEMRA. In clinical studies with ACTEMRA, patients who screened positive for hepatitis were excluded from the study.

2. Gastrointestinal Perforations
Gastrointestinal perforations have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. ACTEMRA should be used with caution in patients at increased risk for gastrointestinal perforation, including those with a history of gastrointestinal ulceration, diverticulitis, concomitant corticosteroid use and age $\geq$ 65 years. These medically confirmed GI perforations occurred at a higher rate following treatment with 8mg/kg ACTEMRA compared to 4mg/kg ACTEMRA [0.20 (95% CI: 0.14, 0.29) vs. 0.14 (95% CI: 0.00, 0.77) per 100 patient years exposure] (see ADVERSE REACTIONS).

Patients should be evaluated promptly for early identification of gastrointestinal perforation, especially since typical symptoms of diverticulitis or perforation such as pain, fever or leukocytosis may be attenuated or absent in immunocompromised patients.
In clinical studies with ACTEMRA, patients with a history of diverticulitis, chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis or other symptomatic lower GI conditions were excluded.

3. Laboratory Abnormalities

Neutrophils
Treatment with ACTEMRA was associated with a higher incidence of neutropenia (see ADVERSE REACTIONS: Hematology Abnormalities). A serious infection has been reported in 1/212 patient with grade 3 treatment-related neutropenia in the long-term extension study.

Caution should be exercised when considering initiation of treatment with ACTEMRA in patients with a low neutrophil count i.e. absolute neutrophil count (ANC) < 2 x 10^9/L. In patients with an absolute neutrophil count < 0.5 x 10^9/L treatment is not recommended (see also DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment).

Neutrophils should be monitored in RA 4 to 8 weeks after start of therapy and thereafter according to good clinical practice (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacodynamics). For recommended modifications based on ANC results, see DOSAGE and ADMINISTRATION.

In pJIA and sJIA: Neutrophils should be monitored prior to the initiation of treatment, at the time of the second infusion and thereafter every 2 to 4 weeks according to good clinical practice (see DOSAGE and ADMINISTRATION, Dose Adjustments for pJIA and sJIA).

Platelets
Treatment with ACTEMRA was associated with a reduction in platelet counts.

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a platelet counts below 100 x $10^3/\mu$l. In patients with a platelet count <50 x $10^3/\mu$l treatment is not recommended (see also DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment).

Platelets should be monitored in RA 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended modifications based on platelet counts, see DOSAGE and ADMINISTRATION.

In pJIA and sJIA: Platelets should be monitored prior to the initiation of treatment, at the time of the second infusion and thereafter every 2 to 4 weeks according to good clinical practice (see DOSAGE and ADMINISTRATION, Dose Adjustments for pJIA and sJIA).

Liver Function Tests
Treatment with ACTEMRA particularly when administered concomitantly with methotrexate, was associated with a higher incidence of mild to severe elevations in hepatic enzymes (see ADVERSE REACTIONS: Liver Enzyme Elevations); therefore caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment.

In clinical trials, one patient who had received ACTEMRA 8 mg per kg monotherapy without elevations in transaminases experienced elevation in AST to above l0x 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.

In clinical trials, mild to severe elevations of hepatic transaminases have been observed with tocilizumab treatment. In the all exposure population, of the 570 patients who reported an elevation >3ULN, 18 patients (3%) also reported a moderate or severe hepatic AEs at any time, of which 10 (1.8%) were reported after the elevation (see ADVERSE REACTIONS: Abnormal Hematologic and Clinical Chemistry Findings).

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 normalization of liver enzymes in 243 of 348 patients (see DOSAGE AND ADMINISTRATION; Dose and Dosage Adjustment).

Increased frequency of these elevations was observed when potential hepatotoxic drugs (e.g. methotrexate (MTX)) were used in combination with tocilizumab.

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with elevated transaminases: ALT or AST > 1.5x ULN**.** In patients with elevated ALT or AST > 5x ULN treatment is not recommended.

ALT and AST should be monitored in RA 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended modifications based on transaminases, see DOSAGE and ADMINISTRATION.

In pJIA and sJIA: ALT and AST should be monitored prior to the initiation of treatment, at the time of the second infusion and thereafter every 2 to 4 weeks according to good clinical practice (see DOSAGE and ADMINISTRATION, Dose Adjustments for pJIA and sJIA).

Lipids

Lipid levels in untreated RA patients tend to be lower compared to the general population as it relates to the increase in systemic inflammation in patients with RA. Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, and/or low density lipoprotein (LDL) cholesterol, (see ADVERSE REACTIONS: Elevations in lipid parameters).

Assessment of lipid parameters should be performed in RA, pJIA and sJIA prior to the initiation of treatment, 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately six-month intervals according to good clinical practice. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

4. Cardiovascular Risk

RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care. Adverse events of hypertension have been observed with ACTEMRA treated patients in clinical trials, 20 hypertension serious adverse events (SAEs) (0.14 per 100 patient years exposure) in long-term trials occurred in patients receiving ACTEMRA, all at the higher dose (8 mg/kg) (see ADVERSE REACTIONS). Most events were transitory.

5. Malignancies

The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies (see ADVERSE REACTIONS: Malignancies). ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies (see ADVERSE REACTIONS, Adverse Drug Reactions Overview, Malignancies).

6. Carcinogenesis and Mutagenesis

No long-term animal studies have been performed to establish the carcinogenicity potential of ACTEMRA. Standard genotoxicity studies with tocilizumab in both prokaryotic and eukaryotic cells were all negative (see TOXICOLOGY).

7. Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of ACTEMRA (see ADVERSE REACTIONS: Infusion Reactions). 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% of patients in the all-exposure rheumatoid arthritis population, and have occurred after multiple infusions.

In the post marketing setting, serious hypersensitivity AEs including death and anaphylaxis occurred during treatment with ACTEMRA, both with or without premedication; and with or without previous hypersensitivity reactions. These SAEs occurred in patients treated with a range of doses of ACTEMRA, and with or without other treatments for arthritis. These events were associated with the first infusion of ACTEMRA and as late as the 20^{th} infusion, although the majority (66/86, 77%) of cases were reported between the 2^{nd} and 4^{th} doses (in cases where the infusion number was reported).

Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with ACTEMRA. ACTEMRA should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis. If an anaphylactic reaction or other serious 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. Patients with clinically significant hypersensitivity should not be rechallenged with additional doses of ACTEMRA (see CONTRAINDICATIONS and ADVERSE REACTIONS).

8. 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. 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.

9. Active Hepatic Disease and Hepatic Impairment:

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment.

10. Immunization:

Live and live attenuated 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. 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 treatment with ACTEMRA. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

11. Dependence/Tolerance

No studies on the effects 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.

12. Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machinery have been performed. However, there is no evidence from the available data that treatment with ACTEMRA affects the ability to drive and use machines.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

13. Macrophage Activation Syndrome (MAS)

MAS is a serious life-threatening disorder that may develop in patients with sJIA. In clinical trials, ACTEMRA has not been studied in patients during an episode of active MAS. Cases of MAS, including a case with a fatal outcome [15 days following the 4th ACTEMRA dose (8 mg/kg)], have been reported in clinical trials. MAS has also been reported in the post-marketing setting.

14. Special Populations

Pregnant Women: There are no adequate data from the use of ACTEMRA in pregnant women. A study in monkeys did not indicate any dysmorphogenic potential but has yielded a higher

number of spontaneous abortions /embryo-foetal deaths at a high dose (see TOXICOLOGY: Animal Toxicology and/or Pharmacology). The relevance of these data for humans is unknown. Of the 33 pregnancies occurring during treatment with ACTEMRA in clinical trials, the outcome is known for 30 cases: 13 had therapeutic terminations, 7 resulted in spontaneous miscarriage, 9 delivered to term with eight healthy newborns and one neonatal death due to ARDS, and one pregnancy was later reported as suspected gestational trophoblastic tumor.

ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Nursing Women: Excretion of a murine analogue of tocilizumab into the milk of lactating mice has been observed, however, it is unknown whether tocilizumab is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with tocilizumab should be made taking into account the benefit of breast-feeding to the child and the benefit of tocilizumab therapy to the woman.

Pediatrics (< 18 years of age): Safety and effectiveness of ACTEMRA in pediatric patients with conditions other than pJIA and sJIA have not been established. Children under the age of two have not been studied.

Geriatrics (> 65 years of age): Of the 2644 patients who received ACTEMRA in studies, 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. There is a higher incidence of infections in the elderly population in general, therefore, caution should be used when treating the elderly with ACTEMRA.

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 also WARNINGS AND PRECAUTIONS, Active Hepatic Disease and Hepatic Impairment).

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.

ADVERSE REACTIONS

RHEUMATOID ARTHRITIS

Adverse Drug Reaction Overview

The ACTEMRA data described below includes 5 Phase III, double-blind, controlled, multicenter studies and their extension periods. In the double-blind controlled studies, patients received doses of ACTEMRA 8 mg/kg monotherapy (288 patients), ACTEMRA 8 mg/kg in combination

with DMARDs (including methotrexate) (1582 patients), or ACTEMRA 4 mg/kg in combination with methotrexate (774 patients).
Safety data is also presented from study II, Lithe, (see CLINICAL TRIALS) from the initial randomized treatment period up to 24 months. This data also contributed to the 6-month controlled study data presented below and in Table 1 and All Exposure data described below.

The all exposure population includes all patients who received at least one dose of ACTEMRA either in the double-blind control period or open label extension phase in studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3309 for at least one year; 2995 received treatment for at least 2 years and 2776 for at least 3 years.

Due to the design of the phase III studies, of the 974 patients who received 4mg/kg as their first dose of ACTEMRA, 836 (86%) also received at least one dose of 8 mg/kg before or at entry into the long term extension studies. Therefore the majority of the safety data is for patients receiving 8 mg/kg dose. Of the total ACTEMRA exposure in the clinical studies 5% was in patients receiving 4 mg/kg and 95% was in patients receiving 8 mg/kg.

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 frequent serious adverse events (SAE) were serious infections, including pneumonia and cellulitis (see WARNINGS AND PRECAUTIONS). The second most frequently reported type of SAE was injury, poisoning, and procedural complications, specifically fractures. The most frequently reported adverse events in 6-month controlled studies (occurring in $\geq$ 3% of patients treated with monotherapy or in combination with traditional DMARDs) were upper respiratory tract infections, headache, nasopharyngitis, urinary tract infections, nausea, hypertension– increased alanine amino transferase (ALT) diarrhea, abdominal pain, dyspepsia, sinusitis, bronchitis, rash, back pain, rheumatoid arthritis, and dizziness.

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.

Infections
In the 6-month controlled studies, the rate of all infections reported in the 4 mg/kg and 8 mg/kg ACTEMRA plus traditional DMARD treatment was 133 and 127 events per 100 patient years, respectively, compared to 112 events per 100 patient years in the placebo plus traditional DMARD group.

In Study II, during the initial randomized treatment up to 12 months, the proportion of patients with an infection was higher in the ACTEMRA + MTX groups compared with the placebo + MTX group (ACTEMRA 4 mg/kg + MTX 46.9%, ACTEMRA 8 mg/kg + MTX 49.9% vs placebo 39.5%) as was the overall rate of infections per 100 patient-years (110.1 and 97.1 vs 92.9 events respectively). In the cumulative data up to 24 months, the profile of infections was

comparable with that reported up to 12 months with no changes in either the type of infections reported or the rates per 100 patient-years. The rates of infections across all treatment groups were highest during the first 6 months of treatment and did not increase over time up to month 24.

The overall rate of infections with ACTEMRA in the all exposure population was 105 events per 100 patient years exposure.

Serious Infections
In the 6-month controlled clinical studies, the rate of serious infections (bacterial, viral and invasive fungal) in the 4 mg/kg and 8mg/kg ACTEMRA plus traditional DMARDs was 4.4 and 5.3 events per 100 patient years, respectively, compared to 3.9 events per 100 patient years exposure in the placebo plus traditional DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the ACTEMRA group and 1.5 events per 100 patient years of exposure in the MTX group.

In Study II, during initial randomized treatment up to 12 months, the proportion of patients with serious infections was infrequent in all three treatment groups (2.5% in the ACTEMRA 4 mg/kg + MTX group, 3.0% in the ACTEMRA 8 mg/kg + MTX group and 1.5% in the placebo + MTX group) as were the rates per 100 patient-years (3.7, 4.0 and 2.3, respectively). Pneumonia was the most commonly reported serious infection in all three groups. Cumulative data up to month 24 demonstrate that the rates of serious infections across all treatment groups were highest during the first 12 months of treatment and did not increase over time.

In the all exposure population, the overall rate of serious infections observed was 4.5 events per 100 patient years exposure. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, urinary tract infection, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Twenty five fatal infections/4009 patients (0.6%) were reported with the most common infections resulting in death being pneumonia and sepsis/septic shock. Infectious agents included: streptococcus, staphylococcus, enterococcus, pseudomonas, blastomycosis and E.coli.

Opportunistic Infections
In the All Exposure population, a total of 34 opportunistic infections were reported in 33 patients. The most common opportunistic infection was pulmonary tuberculosis; sixteen of the 34 opportunistic infections were serious. Of the 34 opportunistic infections, 2 were fatal, and 4 (12%) led to ACTEMRA dose modification. One patient with systemic candida also had concomitant staphylococcal sepsis, which was the cause of death.

In addition, 16 AEs of tuberculosis, 12 of which were SAEs, were reported in 14/4009 patients (13 de novo and 1 reactivation). Fourteen (14) cases of tuberculosis occurred after 24 months of treatment with ACTEMRA [0.16 per 100 patient years exposure, 95% CI (0.09, 0.28)] compared to 2 cases during the first 24 months [0.03 per 100 patient years exposure, 95% CI (0.00, 0.11)] although due to the low numbers of event the increase in the rate of TB events over time cannot be confirmed. The 16 tuberculosis cases (0.11 per 100 patient years) occurred in patients

receiving the higher dose of ACTEMRA, i.e. 8 mg/kg (see ADVERSE EVENTS: Adverse Drug Reaction Overview).

In Study II, five opportunistic infections were reported: Candida osteomyelitis, GI candidiasis, Cryptococcal pneumonia, Pseudomonas and Serratia bursitis, and tuberculous pleurisy. All occurred in patients on ACTEMRA 8 mg/kg, the former two events during the initial 52 weeks of the study.

Gastrointestinal Perforation
During the 6-month controlled clinical trials, the incidence overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with tocilizumab therapy.

In Study II, for the cumulative data up to 24 months, four patients reported GI perforations: one patient receiving ACTEMRA 4 mg/kg + MTX and three patients receiving ACTEMRA 8 mg/kg + MTX. The rate of GI perforation in the ACTEMRA 4 mg/kg and 8 mg/kg groups (0.19 and 0.23 events per 100 patient-years, respectively) is consistent with the overall rates reported below in the all exposure population. Two additional cases of diverticulitis (one serious) were reported in patients receiving ACTEMRA 8 mg/kg.

In the long-term all exposure population the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years. Reports of gastrointestinal perforation on tocilizumab 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: Gastrointestinal Perforations). The relative contribution of these concomitant medications versus ACTEMRA to the development of GI perforations is not known.

Infusion Reactions
In the 6-month controlled clinical studies, adverse events associated with infusion (occurring during or within 24 hours of infusion) were reported in 8% and 7% of patients in the 4 mg/kg and 8 mg/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/kg and 8 mg/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. No premedication were administered in the clinical trials.

Anaphylaxis
Clinically significant hypersensitivity reactions (e.g., anaphylactoid and anaphylactic reactions) associated with ACTEMRA and requiring treatment discontinuation were reported in 0.1% (3/2644) in the 6-month, controlled trials and in 0.2% (8/4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of ACTEMRA (see WARNINGS and PRECAUTIONS: Hypersensitivity Reactions).

In Study II, up to 24 months, four serious anaphylactic reaction or shock events that required treatment discontinuation were reported, all with ACTEMRA 4 mg/kg + MTX treatment. These reactions were all observed in the first 12 months of the study, during the second or third infusion of ACTEMRA. There were in addition, two cases of infusion-associated hypersensitivity reactions (both on ACTEMRA 4 mg/kg + MTX) that led to premature withdrawal from treatment.

Immunogenicity
In 6-month controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty six patients (1.6%) developed positive anti-tocilizumab antibodies of whom 5 had an associated medically significant hypersensitivity reaction leading to withdrawal. Thirty patients (1.1%) developed neutralizing antibodies.

Malignancies
During the 6-month 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 Study II, during the first 52 weeks, one solid tumour was reported in the placebo-MTX group (1/392 patients = <1%). Twelve malignancies where reported in the ACTEMRA groups: (12/798 patients = 1.5%): eight solid tumours (two prostate cancers, two cervical carcinomas and one each of breast cancer, kidney clear cell carcinoma, uterine endometrial cancer, and stage III squamous cell lung carcinoma); and four skin carcinomas.

During the second year (open-label phase), nine solid tumours were reported in the ACTEMRA groups: three lung cancers (lung cancer, metastatic lung adenocarcinoma, and metastatic non-small cell cancer) and one each of anal cancer, metastatic endometrial cancer, gastro-oesophageal cancer, malignant melanoma metastatic to liver, thyroid cancer, metastatic tongue cancer, and squamous cell carcinoma of the skin.

An overall total of 126 malignancies were reported in the All Exposure population up to August 28, 2009. Malignancies represent all histologically-confirmed cases of invasive cancer and are divided in to solid tumours (stage and type unspecified) (including 16 cases of lung cancer, 10 cases of breast cancer, 6 cases of prostate cancer, 4 cases of cervical cancer, 4 cases of gastrointestinal tract cancer, 4 cases of endometrial cancer and 3 cases each of ovarian, colon and sarcomas. Additionally, 2 cases each of thyroid, anal, tongue, carcinoid, gastric, melanoma and transitional cell cancers have been reported and 1 case each of bladder, glioblastoma, respiratory tract, nasal cavity, renal cell and uterine cancer; stage and type unspecified), non-melanoma skin cancers (24 cases of basal cell carcinoma and 12 cases of squamous cell carcinoma and 1 case of basosquamous carcinoma), hematologic cancers (each of acute myeloid leukemia, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and diffuse large B-cell lymphoma stage III, and gammopathy, myelodysplastic syndrome and non-Hodgkin's lymphoma), and other cancers (each of pleural effusion, squamous cell carcinoma and skin cancer).

The rate of malignancies remained consistent (1.15 events per 100 patient years) with the rate observed in the 6-month, controlled period.

Cardiovascular/Hypertension
In study II through 24 months of treatment, hypertension was more common in patients receiving ACTEMRA: 13 events (4.56 per 100 patient years) in patients receiving placebo, 42 events (8.05 per 100 patient years) in patients receiving 4 mg/kg ACTEMRA and 91 events (6.89 per 100 patient years) in patients receiving 8 mg/kg ACTEMRA; event rates for hypertension occurring during or within 24 hours of infusion reactions were: 3 events (1.05 per 100 patient years) in patients receiving placebo, 7 events (1.34 per 100 patient years) in patients receiving 4 mg/kg ACTEMRA and 22 events (1.67 per 100 patient years) in patients receiving 8 mg/kg ACTEMRA respectively.

Deaths
During the placebo-controlled Phase III trials in RA, there were 5 (<1%) deaths among 1454 patients in the placebo group and 5 deaths (<1%) among 2644 patients in the combined ACTEMRA group. There was no predominant cause of death among patients treated with ACTEMRA (cardio-respiratory arrest, gastrointestinal haemorrhage, haemorrhagic stroke, myocardial ischemia, post procedural complication). In the controlled and uncontrolled Phase III RA studies, there were 55 deaths among 4009 patients treated with at least one dose of ACTEMRA over an exposure period of 12293 patient years (0.45 per 100 patient years), and 6 deaths among 1555 placebo patients over an exposure period of 824.56 patient years (0.73 per 100 patient years). The most common causes of death among patients treated with ACTEMRA were myocardial infarction (5 deaths), pulmonary embolism (4 deaths), cardio-respiratory arrest & septic shock (3 deaths each), and suicide, multi-organ failure, pneumonia, sepsis & subarachnoid haemorrhage (2 deaths each).

In study II, a total of 10 deaths were reported (6 during the initial 52-week study period [1 of which occurred on placebo, 4 in 8 mg/kg and 1 in placebo with escape to 4 mg/kg] and 4 during the second 52 weeks of the study, all on ACTEMRA 8 mg/kg, due respectively to gastroesophageal cancer, metastatic malignant melanoma, metastatic lung adenocarcinoma and cardiomyopathy.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 below lists the adverse events (regardless of causality) occurring in ≥1% of patients treated with ACTEMRA during placebo-controlled double-blind rheumatoid arthritis studies.

Table 1: Adverse Events Reported by >1% of Patients Treated with ACTEMRA dosed every 4 weeks during Phase III Rheumatoid Arthritis Placebo-Controlled Studies (6-month control portion)

Body System/Adverse Event	ACTEMRA 8mg/kg monotherapy N = 288 (%)	MTX N=284 (%)	ACTEMRA 4mg/kg + MTX N=774 (%)	ACTEMRA 8mg/kg + DMARDS N=1582 (%)	Placebo + DMARDs N=1170 (%)
Infections and Infestations					
Upper respiratory tract infection	7.3	5.3	6.2	7.8	6.1
Nasopharyngitis	6.9	6.0	4.3	5.6	4.4
Urinary Tract Infection	4.2	4.6	2.2	3.4	3.3
Sinusitis	3.1	3.9	2.1	2.9	2.1
Bronchitis	3.1	2.1	4.3	3.2	3.2
Pharyngitis	2.4	2.1	1.7	1.6	1.7
Influenza	1.7	2.8	2.8	2.5	2.6
Gastroenteritis	1.4	3.2	2.3	1.5	1.5
Oral Herpes	0.7	0.7	1.2	1.4	0.6
Pneumonia	1.0	0.4	1.0	1.0	0.9
Gastroenteritis Viral	1.7	1.4	0.9	0.8	0.6
Herpes Zoster	0.3	--	0.8	1.1	0.7
Rhinitis	0.7	2.1	1.4	0.6	0.5
Cellulitis	0.3	0.4	0.3	1.1	0.7
Cystitis	0.7	0.7	1.2	0.6	0.3
Gastrointestinal Disorders					
Nausea	6.3	12.0	4.3	4.0	3.8
Diarrhea	5.2	5.3	4.0	3.9	3.2
Dyspepsia	3.5	4.2	2.2	2.6	2.0
Mouth Ulceration	2.1	2.1	1.3	2.0	0.5
Abdominal pain, upper	1.7	2.1	2.7	2.5	1.5
Vomiting	2.1	3.2	2.1	1.7	1.6
Abdominal pain	3.8	2.1	1.7	1.3	1.3
Gastritis	1.0	1.8	1.2	1.8	0.8
Constipation	1.4	1.4	1.0	1.2	0.9
Stomatitis	1.4	1.8	0.5	0.8	0.3
Abdominal Discomfort	1.0	--	0.3	0.2	0.2
Skin and Subcutaneous Tissue Disorders					
Rash	2.4	1.4	3.9	3.3	1.3
Pruritus	2.8	1.1	1.4	1.6	0.9
Alopecia	2.1	2.8	0.8	1.0	0.5
Musculoskeletal and Connective Tissue Disorders					
Back Pain	2.4	1.1	2.1	3.3	2.4
Rheumatoid Arthritis	0.7	2.1	3.0	2.1	4.1
Arthralgia	2.4	1.4	1.4	1.1	2.0
Musculoskeletal pain	1.0	0.4	0.8	0.4	0.4
Osteoarthritis	1.4	--	0.3	0.3	0.3
Nervous system disorders					

Body System/Adverse Event	ACTEMRA 8mg/kg monotherapy N = 288 (%)	MTX N=284 (%)	ACTEMRA 4mg/kg + MTX N=774 (%)	ACTEMRA 8mg/kg + DMARDS N=1582 (%)	Placebo + DMARDs N=1170 (%)
Headache	7.3	2.5	5.8	5.3	3.4
Dizziness	3.1	1.4	1.9	3.1	1.7
Paraesthesia	1.0	--	0.4	0.6	0.5
Hypoaesthesia	1.0	0.4	0.5	0.3	0.3
Investigations					
Alanine Aminotransferase increased	5.6	3.9	2.8	3.2	0.9
Transaminases increased	1.0	4.6	1.7	2.3	0.5
Hepatic enzyme increased	2.1	2.8	1.2	1.5	0.6
Weight Increased	1.7	0.4	0.6	0.8	0.2
Aspartate Aminotransferase Increased	1.7	0.4	0.4	0.3	<0.1
Neutrophil Count Decreased	1.0	--	0.3	0.3	--
Blood Triglycerides Increased	1.0	--	--	0.3	--
Vascular Disorders					
Hypertension	5.6	2.1	4.1	4.4	2.7
Flushing	1.0	0.4	0.6	0.3	0.3
General Disorders and Administration Site Conditions					
Fatigue	1.7	3.2	1.4	2.4	2.1
Oedema Peripheral	1.7	--	1.3	2.1	1.5
Pyrexia	0.3	1.1	1.3	0.6	1.6
Asthenia	0.7	0.7	1.0	0.5	0.6
Chest Pain	1.4	1.1	0.8	0.5	0.5
Respiratory, Thoracic and Mediastinal Disorders					
Cough	2.8	0.4	2.1	2.3	1.9
Pharyngolaryngeal Pain	2.4	1.1	1.9	1.7	1.1
Dyspnoea	0.3	0.4	1.0	0.8	0.3
Injury, Poisoning and Procedural Complications					
Fall	0.3	--	1.0	0.7	0.9
Reproductive System and Breast Disorders					
Menorrhagia	1.0	0.4	0.3	0.3	0.3
Renal and Urinary Disorders					
Dysuria	1.7	0.4	0.4	0.4	0.7
Ear and Labyrinth Disorders					
Vertigo	0.7	0.4	1.2	0.7	1.0
Blood and Lymphatic System Disorders					
Leukopenia	1.4	--	0.5	1.2	<0.1
Anaemia	0.3	2.5	0.8	1.0	1.9
Neutropenia	1.4	--	0.4	1.1	--
Metabolism and Nutrition Disorders					

Body System/Adverse Event	ACTEMRA 8mg/kg monotherapy N = 288 (%)	MTX N=284 (%)	ACTEMRA 4mg/kg + MTX N=774 (%)	ACTEMRA 8mg/kg + DMARDS N=1582 (%)	Placebo + DMARDs N=1170 (%)
Hypercholesterolaemia	0.3	0.4	0.3	1.1	--
Hyperlipidaemia	1.4	--	0.4	0.2	0.3
Psychiatric Disorders					
Insomnia	2.1	1.1	2.1	1.0	1.3
Depression	2.1	0.7	1.0	1.3	1.2
Anxiety	2.4	0.7	0.6	0.8	0.8
Eye Disorders					
Conjunctivitis	1.4	0.4	0.6	0.9	0.5

Table 2 below lists the adverse events (regardless of causality) occurring in ≥1% of patients treated with ACTEMRA through 12 months treatment in Study II, Lithe. As patients were allowed to have escape therapy and the data in this table includes adverse events during original treatment group and escape therapy, patients may be represented in more than one treatment group.

Table 2: Adverse Events Reported by >1% of Patients Treated with ACTEMRA dosed every 4 weeks during Study II, Lithe through 12 Months of Treatment (events on escape therapy are included)

Body System/Adverse Event	Placebo + MTX* N=392 (%)	ACTEMRA (Plac→4) 4 mg/kg +MTX N=196$^{\Delta}$ (%)	ACTEMRA (Plac→4→8) 8mg/kg +MTX N=30 $^{\Delta}$ (%)	ACTEMRA (4 and 4→8) 4 mg/kg +MTX* N=399 (%)	ACTEMRA (4→8) 8 mg/kg +MTX N=95$^{¥}$ (%)	ACTEMRA 8 mg/kg+ MTX* N=399 (%)
Infections and Infestations	147 (38)	63 (32)	12 (40)	179 (45)	43 (45)	211 (53)
Upper respiratory tract infection	26(7)	10(5)	1(3)	36(9)	6(6)	49 (12)
Urinary tract infection	21(5)	6(3)	-	20(5)	5(5)	22(6)
Nasopharyngitis	17(4)	10(5)	1(3)	17(4)	5(5)	30(8)
Bronchitis	17(4)	6(3)	1(3)	19(5)	4(4)	22(6)
Influenza	16(4)	2(1)	1(3)	16(4)	5(5)	18(5)
Sinusitis	10(3)	5(3)	-	22(6)	7(7)	14(4)
Pharyngitis	9(2)	4(2)	2(7)	15(4)	4(4)	14(4)
Gastroenteritis	9(2)	5(3)	-	12(3)	3(3)	9(2)
Gastroenteritis viral	8(2)	3(2)	1(3)	10(3)	3(3)	8(2)
Viral upper respiratory tract infection	6(2)	3(2)	-	7(2)	2(2)	4(1)
Cellulitis	5(1)	2(1)	1(3)	3(<1)	-	6(2)
Pneumonia	6(2)	1(<1)	-	5(1)	-	5(1)
Herpes zoster	3(<1)	2(1)	-	4(1)	-	9(2)
Rhinitis	3(<1)	-	-	6(2)	-	6(2)
Tooth abscess	3(<1)	--	-	7(2)	2(2)	2(<1)
Cystitis	2(<1)	2(1)	1(3)	9(2)	3(3)	2(<1)

Body System/Adverse Event	Placebo + MTX* N=392 (%)	ACTEMRA (Plac→4) 4 mg/kg +MTX N=196[Δ] (%)	ACTEMRA (Plac→4→8) 8mg/kg +MTX N=30 [Δ] (%)	ACTEMRA (4 and 4→8) 4 mg/kg +MTX* N=399 (%)	ACTEMRA (4→8) 8 mg/kg +MTX N=95[¥] (%)	ACTEMRA 8 mg/kg+ MTX* N=399 (%)
Respiratory tract infection	-	2(1)	1(3)	10(3)	1(1)	4(1)
Oral Herpes	1(<1)	1(<1)	-	5(1)	1(1)	6(2)
Gastrointestinal Disorders	63 (16)	26 (13)	5 (17)	82 (21)	24 (25)	96 (24)
Nausea	15(4)	5(3)	-	11(3)	4(4)	14(4)
Diarrhea	8(2)	4(2)	-	16(4)	-	15(4)
Dyspepsia	8(2)	5(3)	-	11(3)	3(3)	11(3)
Abdominal pain, upper	8(2)	4(2)	1(3)	11(3)	4(4)	8(2)
Gastritis	5(1)	2(1)	-	11(3)	2(2)	8(2)
Mouth ulceration	3(<1)	-	-	4(1)	2(2)	10(3)
Vomiting	3(<1)	4(2)	1(3)	6(2)	-	7(2)
Constipation	4(1)	1(<1)	-	4(1)	-	9(2)
Abdominal pain	5(1)	3(2)	-	2(<1)	1(1)	7(2)
Haemorrhoids	2(<1)	-	-	1(<1)	-	8(2)
Gastrooesophageal reflux disease	3(<1)	-	-	2(<1)	3(3)	1(<1)
Aphthous Stomatitis	1(<1)	3(2)	-	2(<1)	1(1)	1(<1)
Stomatitis	-	2(1)	-	2(<1)	-	4(1)
Musculoskeletal and Connective Tissue Disorders	50 (13)	16 (8)	3 (10)	60 (15)	14 (15)	72 (18)
Rheumatoid arthritis	15(4)	3(2)	-	9(2)	4(4)	10(3)
Back Pain	8(2)	1(<1)	-	13(3)	1(1)	17(4)
Arthralgia	8(2)	2(1)	-	7(2)	1(1)	12(3)
Osteoarthritis	4(1)	2(1)	-	3(<1)	-	7(2)
Bursitis	-	-	-	3(<1)	-	11(3)
Muscle spasms	4(1)	1(<1)	-	2(<1)	-	3(<1)
Skin and Subcutaneous Tissue Disorders	37 (9)	21 (11)	2 (7)	55 (14)	13 (14)	64 (16)
Rash	3(<1)	6(3)	-	11(3)	3(3)	10(3)
Alopecia	6(2)	1(<1)	1(3)	6(2)	-	3(<1)
Pruritus	3(<1)	1(<1)	-	6(2)	-	2(<1)
Eczema	2(<1)	-	-	2(<1)	-	5(1)
Ecchymosis	1(<1)	2(1)	-	4(1)	1(1)	2(<1)
Urticaria	1(<1)	1(<1)	-	2(<1)	-	6(2)
Investigations	15 (4)	14 (7)	1(3)	43 (11)	13 (14)	76 (19)
Transaminases increased	6(2)	8(4)	-	20(5)	8(8)	30(8)
Alanine Aminotransferase increased	5(1)	2(1)	-	6(2)	2(2)	22(6)
Blood bilirubin increased	-	1(<1)	-	1(<1)	2(2)	6(2)

Body System/Adverse Event	Placebo + MTX* N=392 (%)	ACTEMRA (Plac→4) 4 mg/kg +MTX N=196[Δ] (%)	ACTEMRA (Plac→4→8) 8mg/kg +MTX N=30 [Δ] (%)	ACTEMRA (4 and 4→8) 4 mg/kg +MTX* N=399 (%)	ACTEMRA (4→8) 8 mg/kg +MTX N=95[¥] (%)	ACTEMRA 8 mg/kg+ MTX* N=399 (%)
Injury, Poisoning and Procedural Complications	34 (9)	12 (6)	-	48 (12)	11 (12)	48 (12)
Contusion	7(2)	1(<1)	-	5(1)	3(3)	7(2)
Arthropod bite	2(<1)	1(<1)	-	4(1)	3(3)	7(2)
Excoriation	3(<1)	3(2)	-	3(<1)	-	1(<1)
Joint injury	1(<1)	-	-	4(1)	1(1)	1(<1)
Limb injury	1(<1)	-	-	5(1)	-	1(<1)
Nervous system Disorders	28 (7)	8 (4)	3 (10)	45 (11)	10 (11)	48 (12)
Headache	8(2)	3(2)	-	20(5)	5(5)	19(5)
Dizziness	7(2)	-	-	7(2)	1(1)	9(2)
Carpal tunnel syndrome	1(<1)	1(<1)	-	5(1)	-	2(<1)
Paraesthesia	1(<1)	2(1)	-	2(<1)	2(2)	-
Syncope	-	1(<1)	-	5(1)	-	1(<1)
General Disorders and Administration Site Conditions	30 (8)	13 (7)	1(3)	43 (11)	6 (6)	44 (11)
Oedema peripheral	7(2)	4(2)	-	5(1)	3(3)	14(4)
Fatigue	6(2)	2(1)	-	6(2)	-	11(3)
Asthenia	3(<1)	1(<1)	-	10(3)	1(1)	3(<1)
Pyrexia	6(2)	2(1)	-	2(<1)	2(2)	1(<1)
Chest pain	-	1(<1)	-	6(2)	1(1)	3(<1)
Respiratory, Thoracic and Mediastinal Disorders	25 (6)	13 (7)	-	37 (9)	8 (8)	44 (11)
Cough	11 (3)	2 (1)	-	12 (3)	2 (2)	15 (4)
Oropharyngeal Pain	2 (<1)	3 (2)	-	4 (1)	1 (1)	9 (2)
Epistaxis	2 (<1)	2 (1)	-	-	-	6 (2)
Dyspnoea	-	4 (2)	-	3 (<1)	-	4 (1)
Asthma	1(<1)	-	-	5 (1)	-	1 (<1)
Vascular Disorders	26 (7)	11 (6)	3 (10)	35 (9)	7 (7)	35 (9)
Hypertension	12 (3)	8 (4)	2 (7)	23 (6)	4 (4)	26 (7)
Hypotension	8(2)	-	-	-	-	1(<1)
Haematoma	-	1 (<1)	1(3)	4 (1)	-	2 (<1)
Metabolism and Nutrition Disorders	12 (3)	3 (2)	3 (10)	21 (5)	8 (8)	31 (8)
Hypercholesterol-aemia	4 (1)	1 (<1)	-	4 (1)	-	14 (4)
Diabetes mellitus	2 (<1)	-	1(3)	4 (1)	3 (3)	3 (<1)
Hypokalaemia	2 (<1)	-	2 (7)	2 (<1)	2 (2)	3 (<1)
Psychiatric Disorders	14 (4)	4 (2)	-	23 (6)	5 (5)	25 (6)
Depression	10 (3)	2 (1)	-	7 (2)	2 (2)	11 (3)
Insomnia	2 (<1)	2 (1)	-	9 (2)	2 (2)	8 (2)

Body System/Adverse Event	Placebo + MTX* N=392 (%)	ACTEMRA (Plac→4) 4 mg/kg +MTX N=196[Δ] (%)	ACTEMRA (Plac→4→8) 8mg/kg +MTX N=30 [Δ] (%)	ACTEMRA (4 and 4→8) 4 mg/kg +MTX* N=399 (%)	ACTEMRA (4→8) 8 mg/kg +MTX N=95[¥] (%)	ACTEMRA 8 mg/kg+ MTX* N=399 (%)
Anxiety	3 (<1)	-	-	4 (1)	1 (1)	5 (1)
Blood and Lymphatic System Disorders	16 (4)	2 (1)	-	19 (5)	3 (3)	19 (5)
Anaemia	11 (3)	2 (1)	-	8 (2)	1 (1)	6 (2)
Neutropenia	-	-	-	2 (<1)	1 (1)	6 (2)
Leukopenia,	-	-	-	1(<1)	-	4(1)
Eye Disorders	12 (3)	9 (5)	-	14 (4)	6 (6)	20 (5)
Conjunctivitis	2 (<1)	3 (2)	-	3 (<1)	-	5 (1)
Cataract	1 (<1)	1 (<1)	-	4 (1)	1 (1)	2 (<1)
Dry Eye	-	2 (1)	-	-	-	-
Ear and Labyrinth Disorders	6 (2)	2 (1)	-	11 (3)	1 (1)	14 (4)
Vertigo	2 (<1)	1 (<1)	-	4 (1)	-	7 (2)
Renal and Urinary Disorders	5 (1)	3 (2)	-	9 (2)	1 (1)	12 (3)
Nephrolithiasis	-	2 (1)	-	4 (1)	-	5 (1)
Immune System Disorders	3 (<1)	5 (3)	-	8 (2)	1 (1)	10 (3)
Seasonal allergy	1 (<1)	1 (<1)	-	1 (<1)	-	4 (1)
Hypersensitivity	-	-	-	4 (1)	-	2 (<1)
Anaphylactic shock	-	2(1)	-	-	-	-
Endocrine Disorders	1 (<1)	-	-	4(1)	-	5 (1)
Hypothyroidism	-	-	-	-	-	4 (1)

* These groups represent the original randomized treatment assignments

[Δ] *Represents patients who started on placebo+MTX escaped to ACTEMRA 4 mg/kg; this includes 30 patients who started on MTX+placebo, escaped to 4 mg/kg and then subsequently escaped to 8mg/kg ACTEMRA.*

[¥] *Includes 95 patients who started on 4 mg/kg escaped to 8 mg/kg ACTEMRA*

Serious Adverse Events

Within Study II, Lithe (see CLINICAL TRIALS) during the initial randomized treatment up to month 12, a higher proportion of patients in the ACTEMRA + MTX groups (4 mg/kg dose: 35 (9%); 8 mg/kg dose: 34 (9%)) experienced SAEs compared with the placebo + MTX group (22 (6%)). Regardless of causality, SAEs occurred most frequently in the following body systems: infections (mainly pneumonia), injury and poisoning (primarily fractures of various types), neoplasms, GI disorders, nervous system disorders and cardiac disorders.

Infections and infestations, the most frequently reported SAEs, were observed in 2.5% of patients in the ACTEMRA 4 mg/kg + MTX group, 3.0% of patients in the ACTEMRA 8 mg/kg + MTX group and 1.5% of patients in the placebo + MTX group. Among the ACTEMRA + MTX, groups, neoplasms were more frequent in the ACTEMRA 4 mg/kg + MTX group (2.5%) than in the ACTEMRA 8 mg/kg + MTX group (0.3%).

In the All Exposure population, the rate of SAEs was 14.6 per 100 patient-years. This is consistent with rates seen in the 12 month period of Study II (placebo patients: 10.15 per 100 patient years; 4 mg/kg dose: 12.78 per 100 patient years 8 mg/kg dose: 11.46 per 100 patient years). There was no evidence of an increased risk of SAEs with prolonged exposure to ACTEMRA.

Dose Interruptions

In study II, dose interruptions were permitted for safety reasons (in particular, for active infections and for ALT/AST elevations).

During initial randomized treatment up to week 52, 19% and 22% of patients in the ACTEMRA + MTX groups (4 mg/kg and 8 mg/kg, respectively) compared with 11% of patients in the placebo + MTX group had dose interruptions for AEs. The most common AEs that led to dose interruptions were infections and infestations, which were reported in 12% and 15% of patients in the ACTEMRA + MTX 4 mg and 8 mg groups, respectively, compared with 6.4% in the placebo + MTX group, elevated liver transaminases (3.3% and 5.3% in the ACTEMRA + MTX 4 mg/kg and 8 mg/kg groups, respectively) and GI disorders including mouth ulcers and abdominal pain (1.3% and 1.8% in the ACTEMRA + MTX 4 mg/kg and 8 mg/kg groups, respectively) compared with patients in the placebo + MTX group (1.0% elevated liver transaminases; 0.5% GI disorders).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Other infrequent adverse drug reactions occurring at an incidence of less than 1% in rheumatoid arthritis patients treated with ACTEMRA in placebo-controlled trials (6-month control portion for Studies I through V and the 12 month treatment portion of Study II) were:

Blood and lymphatic system disorders

Neutropenia, Anaemia, Thrombocytopenia, Lymphopenia, Lymphadenopathy, Eosinophilia, Leukaemoid Reaction, Hypocomplementaemia, Haemolysis, Iron Deficiency Anemia

Cardiac disorders

Palpitations, Tachycardia, Arteriosclerosis Coronary Artery, Myocardial Ischaemia, Acute Myocardial Infarction, Arrhythmia, Atrial Fibrillation, Atrioventricular Block First Degree, Cardiac Failure Congestive, Coronary Artery Disease, Coronary Artery Stenosis, Acute Coronary Syndrome, Supraventricular Tachycardia, Sinus Tachycardia, Left Ventricular Hypertrophy, Extrasystoles, Bundle Branch Block Left

Congenital, familial and genetic disorders

Hereditary Hemorrhagic Telangiesctasia, Pyloric Stenosis

Ear and labyrinth disorders

Vertigo, Motion Sickness, Ear Pain, Tinnitus, Hypoacusis, Otorrhoea Cerumen Impaction, Hearing Impaired, Vertigo Positional

Endocrine disorders
Hypothyroidism, Goitre, Autoimmune Thyroiditis, Hyperthyroidism

Eye disorders
Conjunctivitis, Episcleritis, Vision Blurred, Eyelid Oedema, Eye Oedema, Dry Eye, Blepharitis, Eye Pain, Glaucoma, Lacrimation Increased, Ocular Hyperaemia, Conjunctivitis Allergic, Xerophthalmia , Vitreous Floaters, Visual Disturbance, Sicca Syndrome, Eye Haemorrhage, Scleritis, Punctate Keratitis, Keratitis Interstitial, Foreign Body Sensation In Eyes, Eyelids Pruritus, Eye Pruritus, Eye Irritation, Extraocular Muscle Paresis, Dacryoadenitis Acquired, Conjunctival Haemorrhage, Cataract, Ulcerative Keratitis, Blindness Transient, Diplopia, Eye Discharge, Lens Disorder, Macular Degeneration, Presbyopia, Retinal Detachment

Gastrointestinal disorders
Abdominal Pain, Gastritis, Aphthous Stomatitis, Stomatitis, Constipation, Gastrooesophageal Reflux Disease, Abdominal Discomfort, Abdominal Distension, Flatulence, Gingival Bleeding, Glossodynia, Toothache, Gastric Ulcer, Gingival Pain, Gingivitis, Haematochezia, Oesophagitis, Dry Mouth, Frequent Bowel Movements, Gastritis Erosive, Hiatus Hernia, Abdominal Pain Lower, Epigastric Discomfort, Gastrointestinal Disorder, Oral Pain, Pancreatitis, Rectal Haemorrhage, Tongue Ulceration, Dysphagia, Enteritis, Hypoaesthesia Oral, Irritable Bowel Syndrome, Lip Ulceration, Odynophagia, Reflux Oesophagitis, Abdominal Tenderness, Anal Inflammation, Anorectal Disorder, Stomach Discomfort, Oral Mucosal Blistering, Oral Soft Tissue Disorder, Erosive Oesophagitis, Tongue Exfoliation, Tongue Disorder , Tongue Blistering, Sigmoiditis, Periodontitis, Pancreatitis Chronic, Oral Soft Tissue Disorder, Oral Discomfort, Melaena, Malabsorption, Lip Oedema, Large Intestine Perforation, Haemorrhoids, Gingival Ulceration, Gastrointestinal Motility Disorder, Gastrointestinal Pain, Gastrointestinal Perforation, Erosive Esophagitis, Dental Caries, Colitis, Cheilitis, Change Of Bowel Habit, Gastric Disorder, Gastrooesophageal Reflux Disease, Diverticulum (Intestinal), Food Poisoning, Large Intestinal Ulcer, Peptic Ulcer, Duodenal Ulcer, Saliva Gland Enlargement, Stomach Discomfort, Tooth Impacted, Anal Fissure, Diverticular Perforation, Gastric Haemorrhage, Gastrointestinal Inflammation, Inguinal Hernia, Proctalgia

General disorders and administration site conditions
Oedema Peripheral, Pyrexia, Asthenia, Chills, Chest Pain, Infusion Related Reaction, Chest Discomfort, Pain, Impaired Healing, Malaise, Influenza Like Illness, Injection Site Reaction, Injection Site Extravasation, Face Oedema, Oedema, Infusion Site Reaction, Injection Site Haematoma, Feeling Hot And Cold, Chills, Inflammation, Pitting Oedema, Thirst, Temperature Intolerance, Swelling, Sensation Of Foreign Body, Secretion Discharge, Mucosal Ulceration, Mucosal Inflammation, Local Swelling, Injection Site Pain, Injection Site Pruritus, Injection Site Swelling, Infusion Site Pain, Infusion Site Bruising, Hypothermia, Gravitational Oedema, Generalised Oedema, Feeling Hot, Feeling Cold, Drug Withdrawal Syndrome, Drug Intolerance, Pain, Application Site Hypersensitivity, Hyperpyrexia

Hepatobiliary disorders
Hepatotoxicity, Hyperbilirubinaemia, Hepatic Steatosis, Liver Disorder, Hepatomegaly, Hepatic Function Abnormal, Cytolytic Hepatitis, Cholelithiasis, Cholecystitis Acute, Biliary colic

Immune system disorders

Hypersensitivity, Anaphylactic Reaction, Antiphospholipid Syndrome, Allergy to Arthropod Bite, Autoimmune Disorder, Immunodeficiency, Drug Hypersensitivity

Infections and infestations

Oral Herpes, Herpes Zoster, Influenza, Pneumonia, Gastroenteritis, Cellulitis, Cystitis, Rhinitis, Folliculitis, Respiratory Tract Infection, Tonsillitis, Tinea Pedis, Viral Upper Respiratory Tract Infection, Herpes Simplex, Ear Infection, Localised Infection, Vulvovaginal Mycotic Infection, Abscess Limb, Furuncle, Laryngitis, Lower Respiratory Tract Infection, Paronychia, Viral Infection, Eye Infection, Acute Sinusitis, Nail Infection, Onychomycosis, Otitis Media, Rash Pustular, Tooth Abscess, Fungal Skin Infection, Body Tinea, Candidiasis, Cervicitis, Gastroenteritis Viral, Genital Herpes, Labyrinthitis, Pharyngitis Streptococcal, Pseudomonas Infection, Subcutaneous Abscess, Tracheitis, Chronic Sinusitis, Conjunctivitis Bacterial, Erysipelas, Gastrointestinal Infection, Giardiasis, Infection, Infection Parasitic, Osteomyelitis, Otitis Media Acute, Postoperative Wound Infection, Sepsis, Sialoadenitis, Tooth Infection, Herpes Virus Infection, Oral Candidiasis, Purulent Discharge, Pyelonephritis Chronic, Tinea Versicolour, Vulvovaginitis, Acarodermatitis, Alveolar Osteitis, Anal Candidiasis, Arthritis Bacterial, Vaginal Candidiasis, Parasitic Infection Intestinal, Perianal Abscess, Viral Pharyngitis, Vaginitis Gardnerella, Wound Infection, Tracheobronchitis, Tinea Capitis, Staphylococcal Skin Infection, Staphylococcal Infection, Skin Candida, Septic Arthritis Staphylococcal, Respiratory Tract Infection Viral, Pyoderma, Pyelonephritis Acute, Pyelonephritis, Peridiverticular Abscess, Perianal Abscess, Parotitis, Oral Bacterial Infection, Nipple Infection, Pneumonia Necrotizing, Pneumocystis Jiroveci Pneumonia, Nasal Vestibulitis, Nasal Abscess, Nail Bed Infection, Myringitis, Mycobacterium Avium Complex Infection, Mediastinitis, Keratitis Herpetic, Keratitis Bacterial, Infected Skin Ulcer, Infected Insect Bite, Hordeolum, Herpes Simplex Ophthalmic, Hand-Foot-And-Mouth Disease, Gastrointestinal Candidiasis, Fungal Infection, Erythrasma, Enterobiasis, Endocarditis Enterococcal, Diarrhoea Infectious, Dermatitis Infected, Conjunctivitis Viral, Cellulitis Staphylococcal, Bursitis Infective, Pharyngotonsillitis, Bronchopneumonia, Dermatophytosis, Vaginal Infection, Abdominal Abscess, Abdominal Infection, Abscess, Acariasis, Carbuncle, Diverticulitis, Fungal Rash, Gallbladder Empyema, Gastroenteritis Bacterial, Gastroenteritis Salmonella, Infected Sebaceous Cyst, Infected Tenosynovitis, Mastitis, Periorbital Abscess, Septic Shock, Serratia Infection, Soft Tissue Infection, Staphylococcal Abscess, Wound Sepsis

Injury, poisoning and procedural complications

Contusion, Procedural Hypertension, Traumatic Haematoma, Sunburn, Stress Fracture, Spinal Fracture, Skin Laceration, Skin Injury, Postoperative Wound Complication, Hip Fracture, Foot Fracture, Fall, Drug Toxicity, Excoriation, Joint Sprain, Joint Injury, Thermal Burn, Ankle Fracture, Post-Traumatic Pain, Tendon Rupture, Arthropod Sting, Back Injury, Joint Dislocation, Lower Limb Fracture, Meniscus Lesion, Muscle Strain, Rib Fracture, Tooth Injury, Wound, Wound Dehiscence, Wrist Fracture, Animal Bite, Bone Fissure, Burn First Degree, Femur Fracture, Forearm Fracture, Frostbite, Head Injury, Heat Exhaustion, Heat Stroke, Humerus Fracture, Multiple Injuries, Muscle Rupture, Post Gastric Surgery Syndrome, Procedural Nausea, Procedural Vomiting, Pubic Rami Fracture, Radius Fracture, Scratch, Stress Fracture, Tibia Fracture, Tooth Fracture

Investigations
Liver Function Test Abnormal, Weight Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Blood Pressure Increased, Neutrophil Count Decreased, Platelet Count Decreased, White Blood Cell Count Decreased, Blood Triglycerides Increased, Haemoglobin Decreased, Low Density Lipoprotein Increased, Blood Pressure Decreased, Blood Cholesterol Increased, Weight Decreased, Alanine Aminotransferase Abnormal, Blood Creatinine Increased, Alanine Aminotransferase, Blood Alkaline Phosphatase Increased, Blood Bilirubin Unconjugated Increased, Weight Abnormal, White Blood Cells Urine Positive, Serum Ferritin Decreased, Neutrophil Count Abnormal, Heart Rate Increased, Electrocardiogram Repolarisation Abnormality, Electrocardiogram Qt Prolonged, Cardiac Murmur, Body Temperature Increased, Blood Urine Present, Blood Urea Increased, Blood Pressure Diastolic Increased, Blood Pressure Abnormal, Blood Glucose Increased, Blood Count Abnormal, Blood Potassium Decreased, Arteriogram Coronary, Chest X-Ray Abnormal, Electrocardiogram T Wave Inversion, Tuberculosis Skin Test Positive

Metabolism and nutrition disorders
Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, Diabetic Foot, Hypercalcaemia, Dyslipidaemia, Hyperuricaemia, Hypokalaemia, Diabetes Mellitus, Hypoglycaemia, Hypoglycaemia Unconsciousness, Fluid Retention, Anorexia, Lipid Metabolism Disorder, Increased Appetite, Dehydration, Decreased Appetite, Hypernatremia, Electrolyte Imbalance, Gout

Musculoskeletal and connective tissue disorders
Back Pain, Rheumatoid Arthritis, Arthralgia, Muscle Spasms, Myalgia, Pain In Extremity, Joint Swelling, Arthritis, Musculoskeletal Chest Pain, Musculoskeletal Pain, Rheumatoid Nodule, Bursitis, Muscular Weakness, Neck Pain, Osteoarthritis, Tendonitis, Costochondritis, Nodule On Extremity, Rotator Cuff Syndrome, Synovitis, Osteopenia, Muscle Atrophy, Limb Discomfort, Exostosis, Fibromyalgia, Spinal Osteoarthritis, Joint Effusion, Osteoporosis, Intervertebral Disc Protrusion, Musculoskeletal Stiffness, Bunion, Chondromalacia, Groin Pain, Intervertebral Disc Disorder, Joint Stiffness, Lower Extremity Mass, Metatarsalgia, Osteitis, Sjogren's Syndrome, Synovial Cyst, Tendon Pain, Trigger Finger

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Lung Neoplasm, Angiolipoma, Benign Salivary Gland Neoplasm, Uterine Leiomyoma, Thyroid Adenoma, Skin Papilloma, Meningioma, Hepatic Neoplasm, Cervix Carcinoma Stage 0, Basal Cell Carcinoma, Breast Cancer, Prostate Cancer, Seborrhoeic Keratosis, Benign Neoplasm, Cardiac Myxoma, Cervix Carcinoma, Fibroadenoma, Haemangioma of Liver, Infected Naevus, Lung Squamous Cell Carcinoma (Stage Unspecified), Oral Neoplasm Benign, Skin Cancer, Thyroid Neoplasm, Uterine Cancer

Nervous system disorders
Paraesthesia, Hypoaesthesia, Dysgeusia, Migraine, Somnolence, Burning Sensation, Tremor, Carpal Tunnel Syndrome, Haemorrhagic Stroke, Lethargy, Restless Legs Syndrome, Amnesia, Tension Headache, Syncope, Sinus Headache, Neuropathy Peripheral, Neuralgia, Lumbar Radiculopathy, Ischaemic Cerebral Infarction, Grand Mal Convulsion, Facial Palsy, Dyslexia, Dysaesthesia, Dementia, Cerebrovascular Accident, Carotid Artery Occlusion, Carotid Artery

Stenosis, Dementia Alzheimer's Type, Diabetic Neuropathy, Nerve Compression, Parosmia, Hypertensive Nephropathy, Peripheral Sensorimotor Neuropathy, Presyncope, Syncope Vasovagal

Psychiatric disorders
Insomnia, Anxiety, Depression, Libido Decreased, Neurosis, Nervousness, Major Depression, Confusional State, Sleep Disorder

Renal and urinary disorders
Dysuria, Renal Colic, Calculus Ureteric, Haematuria, Hydronephrosis, Nephrolithiasis, Pollakiuria, Renal Failure, Renal Failure Chronic, Renal Cyst, Polyuria, Micturition Urgency, Leukocyturia

Reproductive System and Breast Disorders
Menorrhagia, Amenorrhoea, Breast Pain, Vaginal Haemorrhage, Benign Prostatic Hyperplasia, Breast Mass, Cervical Dysplasia, Dysmenorrhea, Genital Discharge, Uterine Haemorrhage, Vulval Ulceration, Vaginal Ulceration, Vaginal Discharge, Vaginal Burning Sensation, Ovarian Cyst, Metrorrhagia, Menstruation Irregular, Nipple Pain, Postmenopausal Haemorrhage, Uterine Polyp, Vulvovaginal Pruritus, Menstrual Disorder, Hypomenorrhoea, Genital Haemorrhage, Breast Swelling

Respiratory, thoracic and mediastinal disorders
Dyspnoea, Dyspnoea Exertional, Epistaxis, Rhinitis Allergic, Nasal Congestion, Sinus Congestion, Asthma, Rhinorrhoea, Chronic Obstructive Pulmonary Disease, Interstitial Lung Disease, Nasal Ulcer, Nasal Discomfort, Nasal Dryness, Respiratory Tract Congestion, Vasomotor Rhinitis, Sinusitis Noninfective, Rhinitis Atrophic, Respiratory Tract Irritation, Respiratory Disorder, Pleuritic Pain, Pleurisy, Pleural Effusion, Pharyngeal Inflammation, Nasal Septum Perforation, Idiopathic Pulmonary Fibrosis, Dysphonia, Productive Cough, Rhinorrhoea, Sleep Apnoea Syndrome, Upper Respiratory Tract Inflammation, Aspiration, Bullous Lung Disease, Rales

Skin and subcutaneous tissue disorders
Alopecia, Hyperhidrosis, Rash Papular, Urticaria, Rash Erythematous, Skin Ulcer, Dermatitis, Increased Tendency To Bruise, Dermatitis Allergic, Eczema, Rash Pruritic, Erythema, Night Sweats, Petechiae, Rash Macular, Blister, Dry Skin, Ecchymosis, Drug Eruption, Acne, Pruritus Generalised, Rosacea, Skin Lesion, Swelling Face, Cold Sweat, Erythema Nodosum, Ingrowing Nail, Rash Maculo-Papular, Skin Fragility, Skin Nodule, Stasis Dermatitis, Vasculitic Rash, Angioedema, Cutaneous Vasculitis, Dyspnoea Exertional, Hyperkeratosis, Photosensitivity Reaction, Pityriasis, Psoriasis, Purpura, Skin Hyperpigmentation, Acrodermatitis, Acute Febrile Neutrophilic Dermatosis, Urticaria Generalised, Urticaria Generalised, Skin Exfoliation, Skin Discolouration, Skin Atrophy, Scab, Rash Vesicular, Rash Generalized, Pruritus Allergic, Pityriasis Rosea, Perivascular Dermatitis, Panniculitis, Palpable Purpura, Livedo Reticularis, Leukocytoclastic Vasculitis, Hypoaesthesia Facial, Erythema Multiforme, Erythema Annulare, Dyshidrosis, Dermatitis Contact, Dermatitis Bullous, Decubitus Ulcer, Blood Blister, Actinic Keratosis, Ephelides, Neurodermatitis, Pyoderma Gangrenosum, Seborrhoeic Dermatitis, Skin Fissures, Skin Irritation, Skin Nodule

Vascular disorders
Flushing, Hypotension, Hot Flush, Vasculitis, Haematoma, Varicose Vein, Raynaud's Phenomenon, Phlebitis, Orthostatic Hypotension, Essential Hypertension, Thrombophlebitis Superficial, Vascular Fragility, Venous Stasis, Phlebitis Superficial, Varicophlebitis, Vascular Rupture

Monotherapy: ACTEMRA versus HUMIRA®
In study WA19924, a 24 week randomized, double-blinded, parallel study monotherapy with ACTEMRA 8 mg/kg IV q4w (N=162) was compared to HUMIRA 40 mg SC q2w (N=162).

Serious Adverse Events
The proportion of patients with serious adverse events was ACTEMRA 11.7% vs. HUMIRA 9.9% with the most common event being infections [3.1% (5) each]. In the cases where an organism was identified and reported, the infectious agents were: *Escherichia coli* (urinary tract infection), gram negative cocci (urosepsis) and *staphylococcus aureus* (cellulitis).

Immunogenicity testing was event driven and was not done routinely in either arm of the trial. Patients were identified for anti-TCZ antibody testing if they had an event of anaphylaxis or a serious hypersensitivity reaction that the investigator considered potentially related to ACTEMRA.

There were no events of anaphylaxis and one SAE of drug hypersensitivity in a patient in the HUMIRA arm whose reaction occurred while receiving commercial ACTEMRA (following withdrawal from the trial). One patient in the ACTEMRA arm was withdrawn for an infusion-related reaction (IRR). Only the patient with the IRR had pre- and post-event samples available for immunogenicity testing and tested positive for anti-TCZ antibodies.

Two deaths were reported during the study. Both patients were in the ACTEMRA treatment group. The first patient died suddenly and the cause of death is unknown. The investigator attributed the cause of death in the second patient to an illicit drug overdose.

Dose Interruptions
More patients in the ACTEMRA arm [25% (40 patients)] compared with the HUMIRA arm [19% (30 patients)] had a dose modification or interruption due to AEs. This included 15% of ACTEMRA vs. 12% of HUMIRA patients with an AE of infection, 3% of ACTEMRA vs. 1.2% of HUMIRA patients with an AE of transaminase elevation, and 1.2% of ACTEMRA vs. 0% of HUMIRA patients with an AE of neutropenia.

The proportion of patients who prematurely discontinued treatment was 18% (30 patients) in the HUMIRA arm and 15% (24 patients) in the ACTEMRA arm.

Abnormal Laboratory Findings
The magnitude of change and the frequency of marked laboratory abnormalities was higher with ACTEMRA compared with HUMIRA and occurred more commonly during the first month of treatment. Low neutrophil counts ($<1.5 \times 10^9$/L) were more common in the ACTEMRA arm (14% ACTEMRA vs. 5% HUMIRA). Four (2.5%) patients in the ACTEMRA arm and two

(1.2%) patients in the HUMIRA arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the ACTEMRA arm and five (3.1%) patients in the HUMIRA arm experienced ALT increases of CTC grade 2 or higher) including 2 patients in each treatment group with grade 3 or higher. Four (2.5%) patients in the ACTEMRA arm and two (1.2%) patients in the HUMIRA arm experienced AST increases of CTC grade 2 and 1 patient in the HUMIRA arm experienced AST increases of CTC grade 3.

In patients not receiving lipid lowering agents during the study, the mean LDL increase from baseline was 0.64 mmol/l for patients in the ACTEMRA arm and 0.19 mmol/l for patients in the HUMIRA arm. Twenty-three (19.5%) patients in the ACTEMRA arm and ten (8%) patients in the HUMIRA arm had a week 24 LDL > 4.2mmol/l.

The safety observed in the ACTEMRA arm was consistent with the known safety profile of ACTEMRA (see Table 1) (see CLINICAL TRIALS). Table 3 below lists the adverse events (regardless of causality) occurring in ≥1% of patients in either treatment arm through 24 weeks of treatment.

Table 3: Adverse Events (regardless of causality) Occurring in >1% of Patients in Either Treatment Arm through 24 Weeks of Treatment in Study WA19924

Body System/Adverse Event	HUMIRA 40mg + Placebo (IV) N = 162 No. (%)	ACTEMRA 8mg/kg + Placebo (SC) N = 162 No. (%)
Infections and Infestations		
Total Pts With at Least one AE	68 (42.0)	77 (47.5)
Upper respiratory tract infection	17 (10.5)	18 (11.1)
Nasopharyngitis	13 (8.0)	17 (10.5)
Urinary Tract Infection	11 (6.8)	9 (5.6)
Bronchitis	4 (2.5)	7 (4.3)
Sinusitis	6 (3.7)	5 (3.1)
Gastroenteritis	3 (1.9)	5 (3.1)
Pharyngitis	4 (2.5)	2 (1.2)
Influenza	3 (1.9)	2 (1.2)
Lower respiratory tract infection	2 (1.2)	2 (1.2)
Oral herpes	3 (1.9)	1 (0.6)
Tooth abscess	3 (1.9)	1 (0.6)
Cellulitis	2 (1.2)	1 (0.6)
Cystitis	1 (0.6)	2 (1.2)
Fungal infection	1 (0.6)	2 (1.2)
Gastroenteritis viral	2 (1.2)	1 (0.6)
Localised infection	-	3 (1.9)
Tinea Pedis	2 (1.2)	1 (0.6)
Tonsillitis	-	3 (1.9)
Viral upper respiratory tract infection	1 (0.6)	2 (1.2)
Fungal skin infection	2 (1.2)	-
Herpes simplex	2 (1.2)	-
Pharyngitis streptococcal	2 (1.2)	-
Pharyngotonsillitis	2 (1.2)	-
Vaginal infection	-	2 (1.2)

Body System/Adverse Event	HUMIRA 40mg + Placebo (IV) N = 162 No. (%)	ACTEMRA 8mg/kg + Placebo (SC) N = 162 No. (%)
Vulvovaginal candidiasis	-	2 (1.2)
Musculoskeletal and Connective Tissue Disorders		
Total Pts With at Least one AE	48 (29.6)	43 (26.5)
Rheumatoid arthritis	16 (9.9)	11 (6.8)
Back pain	4 (2.5)	7 (4.3)
Arthralgia	2 (1.2)	6 (3.7)
Muscle spasms	4 (2.5)	3 (1.9)
Musculoskeletal pain	2 (1.2)	3 (1.9)
Myalgia	1 (0.6)	4 (2.5)
Osteoarthritis	3 (1.9)	2 (1.2)
Bursitis	1 (0.6)	3 (1.9)
Connective tissue disorder	2 (1.2)	1 (0.6)
Joint swelling	2 (1.2)	1 (0.6)
Rotator cuff syndrome	2 (1.2)	1 (0.6)
Synovitis	2 (1.2)	1 (0.6)
Intervertebral disc protrusion	-	2 (1.2)
Tendon calcification	2 (1.2)	-
Torticollis	2 (1.2)	-
Gastrointestinal Disorders		
Total Pts With at Least one AE	35 (21.6)	28 (17.3)
Nausea	10 (6.2)	6 (3.7)
Diarrhoea	8 (4.9)	5 (3.1)
Dyspepsia	3 (1.9)	4 (2.5)
Gastrooesophageal reflux Disease	4 (2.5)	1 (0.6)
Abdominal pain	3 (1.9)	1 (0.6)
Aphthous stomatitis	1 (0.6)	3 (1.9)
Abdominal distension	1 (0.6)	2 (1.2)
Abdominal pain upper	2 (1.2)	1 (0.6)
Constipation	3 (1.9)	-
Haemorrhoids	-	3 (1.9)
Mouth ulceration	-	3 (1.9)
Vomiting	2 (1.2)	1 (0.6)
Dental caries	2 (1.2)	-
Skin and Subcutaneous Tissue Disorders		
Total Pts With at Least one AE	25 (15.4)	26 (16.0)
Rash	8 (4.9)	3 (1.9)
Pruritus	7 (4.3)	3 (1.9)
Erythema	3 (1.9)	3 (1.9)
Alopecia	1 (0.6)	3 (1.9)
Dermatitis allergic	2 (1.2)	2 (1.2)
Urticaria	3 (1.9)	1 (0.6)
Hyperhidrosis	1 (0.6)	2 (1.2)
Ingrowing nail	-	2 (1.2)
Swelling face	-	2 (1.2)
General Disorders and Administration Site Conditions		
Total Pts With at Least one AE	32 (19.8)	16 (9.9)
Fatigue	8 (4.9)	5 (3.1)
Oedema peripheral	8 (4.9)	3 (1.9)

Body System/Adverse Event	HUMIRA 40mg + Placebo (IV) N = 162 No. (%)	ACTEMRA 8mg/kg + Placebo (SC) N = 162 No. (%)
Injection site reaction	4 (2.5)	-
Injection site erythema	3 (1.9)	-
Pain	1 (0.6)	2 (1.2)
Chest discomfort	-	2 (1.2)
Injection site hypersensitivity	2 (1.2)	-
Injection site rash	2 (1.2)	-
Respiratory, Thoracic and Mediastinal Disorders		
Total Pts With at Least one AE	26 (16.0)	16 (9.9)
Cough	9 (5.6)	4 (2.5)
Dyspnoea	5 (3.1)	1 (0.6)
Oropharyngeal pain	3 (1.9)	2 (1.2)
Epistaxis	4 (2.5)	-
Rhinitis allergic	4 (2.5)	-
Nasal congestion	2 (1.2)	-
Rhinorrhoea	2 (1.2)	-
Nervous system disorders		
Total Pts With at Least one AE	20 (12.3)	21 (13.0)
Headache	9 (5.6)	9 (5.6)
Dizziness	3 (1.9)	3 (1.9)
Migraine	2 (1.2)	1 (0.6)
Paraesthesia	2 (1.2)	1 (0.6)
Carpal tunnel syndrome	-	2 (1.2)
Injury, Poisoning and Procedural Complications		
Total Pts With at Least one AE	17 (10.5)	19 (11.7)
Contusion	2 (1.2)	3 (1.9)
Ligament sprain	4 (2.5)	1 (0.6)
Arthropod bite	2 (1.2)	1 (0.6)
Fall	2 (1.2)	1 (0.6)
Infusion related reaction	1 (0.6)	2 (1.2)
Muscle strain	1 (0.6)	2 (1.2)
Excoriation	-	2 (1.2)
Investigations		
Total Pts With at Least one AE	10 (6.2)	22 (13.6)
Weight increased	4 (2.5)	5 (3.1)
Alanine aminotransferase increased	2 (1.2)	5 (3.1)
Aspartate aminotransferase increased	2 (1.2)	2 (1.2)
Transaminases increased	1 (0.6)	3 (1.9)
Liver function test abnormal	1 (0.6)	2 (1.2)
Blood cholesterol increased	-	2 (1.2)
Metabolism and Nutrition Disorders		
Total Pts With at Least one AE	14 (8.6)	13 (8.0)
Hypercholesterolaemia	3 (1.9)	4 (2.5)
Hyperlipidaemia	3 (1.9)	3 (1.9)
Diabetes mellitus	2 (1.2)	1 (0.6)
Dyslipidaemia	-	3 (1.9)
Hypokalaemia	2 (1.2)	-
Vascular Disorders		

Body System/Adverse Event	HUMIRA 40mg + Placebo (IV) N = 162 No. (%)	ACTEMRA 8mg/kg + Placebo (SC) N = 162 No. (%)
Total Pts With at Least one AE	12 (7.4)	14 (8.6)
Hypertension	7 (4.3)	13 (8.0)
Hot flush	2 (1.2)	-
Venous insufficiency	2 (1.2)	-
Cardiac disorders		
Total Pts With at Least one AE	8 (4.9)	4 (2.5)
Myocardial infarction	2 (1.2)	1 (0.6)
Immune System Disorders		
Total Pts With at Least one AE	6 (3.7)	6 (3.7)
Hypersensitivity	5 (3.1)	4 (2.5)
Renal and Urinary Disorders		
Total Pts With at Least one AE	7 (4.3)	5 (3.1)
Dysuria	2 (1.2)	1 (0.6)
Eye Disorders		
Total Pts With at Least one AE	4 (2.5)	7 (4.3)
Dry eye	-	2 (1.2)
Blood and Lymphatic System Disorders		
Total Pts With at Least one AE	5 (3.1)	5 (3.1)
Anaemia	2 (1.2)	1 (0.6)
Neutropenia	1 (0.6)	2 (1.2)
Thrombocytopenia	-	2 (1.2)
Psychiatric Disorders		
Total Pts With at Least one AE	3 (1.9)	6 (3.7)
Insomnia	1 (0.6)	3 (1.9)
Depression	1 (0.6)	2 (1.2)
Hepatobiliary Disorders		
Total Pts With at Least one AE	1 (0.6)	2 (1.2)
Hepatic steatosis	-	2 (1.2)

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

The safety of ACTEMRA was studied in 188 pediatric patients, 2 to 17 years of age, with pJIA, with 87 patients treated up to one year.

Through part II of the study, seven patients were withdrawn from the study due to an adverse event (AE). This included 2 SAEs [hypertransaminasemia and benign intracranial hypertension; both in the 8 mg/kg (≥30 kg group)], serum-sickness-like reaction [8 mg/kg (<30 kg group)], pneumonia [8 mg/kg (≥30 kg group)], hyperbilirubinemia [10 mg/kg (<30 kg group)], 1 patient who was withdrawn following an event reported as lack of efficacy [8 mg/kg (<30 kg)], and 1 patient with gastroenteritis that began when the patient had received placebo for 22 weeks in Part II of the study.

Table 5 lists the adverse events (judged to be at least remotely causally-related to treatment) occurring in ≥ 1% of patients treated with ACTEMRA during the Part I (Open label ACTEMRA lead-in portion) of the pJIA trial.

Table 6 lists the adverse events (judged to be at least remotely causally-related to treatment) occurring in ≥ 1% of patients treated with ACTEMRA during the Part II (double-blind placebo-controlled portion) of the pJIA trial.

A total of 159/188 patients reported at least 1 AE, with an overall rate of 479.8 AEs per 100 patient-years. The number of patients experiencing at least 1 AE were 102/119 (85.7%) patients ≥ 30 kg [(ACTEMRA 8 mg/kg) 501.9 per 100 patient-years], 26/28 (92.9%) patients < 30 kg [(ACTEMRA 10 mg/kg), 445.6 per 100 patient-years] and 26/34 (76.5%) patients < 30 kg [(ACTEMRA 8 mg/kg), 471.9 per 100 patient-years]. The highest AE rate was seen in the system organ class (SOC) of infections and infestations.

The majority of AEs were of mild [493 AEs in 139 patients (73.9%)] or moderate [185 AEs in 90 patients (47.9%)] intensity. Sixteen AEs in 16 patients were considered severe in intensity (8.5%).

Serious Adverse Events
Seventeen patients (9.0%) reported 22 serious adverse events (SAEs). The SOC that had the most patients reporting at least 1 SAE in the all exposure population was infections and infestations [9 patients (4.8%)], followed by injury, poisoning and procedural complications [3 patients (1.6%)]. Pneumonia was reported in 4 patients [3 patients receiving ACTEMRA 8 mg/kg (≥ 30 kg) and 1 patient receiving ACTEMRA 10 mg/kg (< 30 kg)]. Bronchitis was reported in 2 patients receiving ACTEMRA 10 mg/kg (< 30 kg) and cellulitis was reported in 2 patients receiving ACTEMRA 8 mg/kg (≥ 30 kg). Individual serious cases of varicella, neck injury, synovial rupture, upper limb fracture, sclerosing cholangitis, hypertransaminasemia, back pain, osteoporosis, familial mediterranean fever, uveitis, constipation, benign intracranial hypertension, psychosomatic disease and urinary calculus were reported. Of the 22 SAEs reported, 5 SAEs that occurred in 5 patients (2.7%) were considered possibly related to study drug by the investigator (benign intracranial hypertension, uveitis, urinary calculus, pneumonia, and cellulitis).

Dose Interruptions
Patients were allowed to have dose interruptions for safety reasons. In the all exposure population, 12.8% of patients experienced ACTEMRA dose interruptions because of safety concerns. There was a higher incidence of AEs leading to dose interruptions in patients receiving ACTEMRA 10 mg/kg (< 30 kg) (28.6%) than patients receiving ACTEMRA 8 mg/kg (< 30 kg) (5.9%) or ACTEMRA 8 mg/kg (≥30 kg) (10.9%). The most common AEs that led to dose interruptions were infections and infestations (9.0%) including pneumonia [5 patients, 2 in patients receiving 10 mg/kg (< 30 kg) and 3 in patients receiving 8 mg/kg (≥30 kg)], pharyngitis streptococcal [1 patient receiving 10 mg/kg (< 30 kg) and 1 patient receiving 8 mg/kg (≥30 kg)] , urinary tract infection [1 patient receiving 10 mg/kg (< 30 kg) and 1 patient receiving 8 mg/kg (<30 kg)] and varicella [1 patient receiving 8 mg/kg (< 30 kg) and 1 patient receiving 8 mg/kg (≥30 kg)].

Infections
The incidence and rate of infections in the ACTEMRA all exposure population was 115/188 patients (61.2%; 163.7 per 100 patient years). Specifically for each dose the incidences were

76/119 (63.9%) patients ≥ 30 kg [(ACTEMRA 8 mg/kg) 160.6 per 100 patient-years], 19/28 (67.9%) patients < 30 kg [(ACTEMRA 10 mg/kg), 198.5 per 100 patient-years] and 16/34 (47.1%) patients < 30 kg [(ACTEMRA 8 mg/kg), 177.0 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 <30 kg treated with 10 mg/kg ACTEMRA (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg ACTEMRA (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg ACTEMRA (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg ACTEMRA (7.6%).

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 (5.9%) experienced infusion reactions 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 within 24 hours of infusion were dizziness and hypotension. Table 4 below summarizes the incidence of infusion reactions by dose/weight.

Table 4 Incidence of Infusion Reactions by Dose/Weight in the All-Exposure Population

	ACTEMRA 10 mg/kg (< 30 kg) N = 28* No. (%)	**ACTEMRA 8 mg/kg (< 30 kg) N = 34 No. (%)**	**ACTEMRA 8 mg/kg (≥ 30 kg) N = 119 No. (%)**	**ACTEMRA All N = 188 No. (%)**
Patients with Event during Infusion	1 (3.6)	3 (8.8)	6 (5.0)	11 (5.9)
Patients with Event within 24 hours of Infusion	2 (7.1)	5 (14.7)	29 (24.4)	38 (20.2)

*Excludes patients who switched to 8 mg/kg

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

In the clinical trial, pJIA patients were not premedicated for the prevention of infusion reactions however oral corticosteroids were used concomitantly by 51% of patients and use was similar across treatment groups (all exposure safety population).

Immunogenicity
One patient in the 10 mg/kg (<30 kg) group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.

Table 5: Adverse Events (judged to be at least remotely causally-related to treatment) Reported by ≥1% of Patients Treated with ACTEMRA dosed every 4 weeks during the Part I (Open label ACTEMRA lead-in phase) of the pJIA trial

Body System / Adverse Event (preferred Term)	ACTEMRA 10 mg/kg (< 30 kg) N = 35	ACTEMRA 8 mg/kg (< 30 kg) N = 34	ACTEMRA 8 mg/kg (≥ 30 kg) N = 119	ACTEMRA All N = 188
Infections and Infestations	4 (11.4)	4 (11.8)	13 (10.9)	21 (11.2)
Nasopharyngitis	2 (5.7)	1 (2.9)	1 (0.8)	4 (2.1)
Rhinitis	1 (2.9)	2 (5.9)	1 (0.8)	4 (2.1)
Upper respiratory tract infection	1 (2.9)		3 (2.5)	4 (2.1)
Influenza	1 (2.9)		1 (0.8)	2 (1.1)
Tonsillitis	1 (2.9)			1 (0.5)
Tracheobronchitis	1 (2.9)			1 (0.5)
Mumps		1 (2.9)		1 (0.5)
Paronychia		1 (2.9)		1 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	4 (11.4)	2 (5.9)	4 (3.4)	10 (5.3)
Cough	1 (2.9)		1 (0.8)	2 (1.1)
Epistaxis	1 (2.9)		1 (0.8)	2 (1.1)
Respiratory tract congestion	1 (2.9)			1 (0.5)
Rhinorrhoea	1 (2.9)			1 (0.5)
Oropharyngeal pain		2 (5.9)	2 (1.7)	4 (2.1)
Gastrointestinal Disorders	-	4 (11.8)	11 (9.2)	15 (8.0)
Nausea		1 (2.9)	6 (5.0)	7 (3.7)
Abdominal pain upper		1 (2.9)	1 (0.8)	2 (1.1)
Gingivitis		1 (2.9)		1 (0.5)
Mouth ulceration		1 (2.9)	3 (2.5)	4 (2.1)
Tongue ulceration		1 (2.9)		1 (0.5)
Vomiting		1 (2.9)		1 (0.5)
Diarrhoea			3 (2.5)	3 (1.6)
Nervous System Disorders	-	2 (5.9)	10 (8.4)	12 (6.4)
Headache		2 (5.9)	4 (3.4)	6 (3.2)
Dizziness			4 (3.4)	4 (2.1)
Eye Disorders	-	2 (5.9)	-	2 (1.1)
Iridocyclitis		1 (2.9)		1 (0.5)
Conjunctivitis		1 (2.9)		1 (0.5)

Body System / Adverse Event (preferred Term)	ACTEMRA 10 mg/kg (< 30 kg) N = 35	ACTEMRA 8 mg/kg (< 30 kg) N = 34	ACTEMRA 8 mg/kg (≥ 30 kg) N = 119	ACTEMRA All N = 188
Musculoskeletal and Connective Tissue Disorders	2 (5.7)	1 (2.9)	3 (2.5)	6 (3.2)
Juvenile arthritis	1 (2.9)	1 (2.9)		2 (1.1)
Polyarthritis	1 (2.9)			1 (0.5)
Skin and Subcutaneous Tissue Disorders	1 (2.9)	2 (5.9)	7 (5.9)	10 (5.3)
Rash macular	1 (2.9)			1 (0.5)
Acne		1 (2.9)		1 (0.5)
Rash		1 (2.9)	2 (1.7)	3 (1.6)
Urticaria			2 (1.7)	2 (1.1)
Pruritis			3 (2.5)	3 (1.6)
Vascular Disorders	1 (2.9)	1 (2.9)	3 (2.5)	5 (2.7)
Hypotension	1 (2.9)	1 (2.9)	1 (0.8)	3 (1.6)
Injury, Poisoning and Procedural Complications	-	1 (2.9)	1 (0.8)	2 (1.1)
Ligament sprain		1 (2.9)		1 (0.5)
General Disorders and Administration Site Conditions	-	1 (2.9)	5 (4.2)	6 (3.2)
Fatigue		1 (2.9)	1 (0.8)	2 (1.1)
Pyrexia			2 (1.7)	2 (1.1)
Immune System Disorders	-	1 (2.9)	-	1 (0.5)
Serum sickness-like reaction		1 (2.9)		1 (0.5)

Table 6: Adverse Events (judged to be at least remotely causally-related to treatment) Reported by ≥1% of Patients Treated with ACTEMRA dosed every 4 weeks during the Part II (double-blind, placebo-controlled phase) of the pJIA trial

Body System / Adverse Event (preferred Term)	Placebo N = 81	ACTEMRA 10 mg/kg (< 30 kg) N = 16	ACTEMRA 8 mg/kg (< 30 kg) N = 11	ACTEMRA 8 mg/kg (≥ 30 kg) N = 55	ACTEMRA All N = 82
Infections and Infestations	14 (17.3)	1 (6.3)	1 (9.1)	11 (20.0)	13 (15.9)
Nasopharyngitis	7 (8.6)			2 (3.6)	2 (2.4)
Influenza	1 (1.2)				
Fungal skin infection	1 (1.2)				
Gastroenteritis	1 (1.2)				
Oral herpes	1 (1.2)				
Sinusitis	2 (2.5)				
Urinary tract infection	2 (2.5)			1 (1.8)	1 (1.2)

Body System / Adverse Event (preferred Term)	**Placebo N = 81**	**ACTEMRA 10 mg/kg (< 30 kg) N = 16**	**ACTEMRA 8 mg/kg (< 30 kg) N = 11**	**ACTEMRA 8 mg/kg (≥ 30 kg) N = 55**	**ACTEMRA All N = 82**
Viral infection	1 (1.2)				
Hordeolum	1 (1.2)				
Paronychia	1 (1.2)				
Abcess limb		1 (6.3)			1 (1.2)
Muscle abcess		1 (6.3)			1 (1.2)
Sinusitis		1 (6.3)			1 (1.2)
Pharyngitis			1 (9.1)		1 (1.2)
Pulpitis dental			1 (9.1)		1 (1.2)
Upper respiratory tract infection				1 (1.8)	1 (1.2)
Rhinitis				1 (1.8)	1 (1.2)
Candidiasis				1 (1.8)	1 (1.2)
Ear infection				1 (1.8)	1 (1.2)
Lower respiratory tract infection				1 (1.8)	1 (1.2)
Otitis media				1 (1.8)	1 (1.2)
Pneumonia				1 (1.8)	1 (1.2)
Pyoderma				1 (1.8)	1 (1.2)
Tonsillitis				1 (1.8)	1 (1.2)
Viral upper respiratory tract infection				1 (1.8)	1 (1.2)
Musculoskeletal and Connective Tissue Disorders	7 (8.6)	-	-	7 (12.7)	7 (8.5)
Juvenile arthritis	6 (7.4)			5 (9.1)	5 (6.1)
Arthritis	1 (1.2)				
Arthralgia				1 (1.8)	1 (1.2)
Myalgia				1 (1.8)	1 (1.2)
Gastrointestinal Disorders	7 (8.6)	-	-	3 (5.5)	3 (3.7)
Abdominal pain upper	2 (2.5)			1 (1.8)	1 (1.2)
Diarrhoea	1 (1.2)				
Abdominal pain	1 (1.2)				
Constipation	1 (1.2)				
Nausea	1 (1.2)				
Oesophagitis	1 (1.2)				
Aphthous stomatitis				1 (1.8)	1 (1.2)
Mouth ulceration				1 (1.8)	1 (1.2)
Gastritis				1 (1.8)	1 (1.2)
Respiratory, Thoracic and Mediastinal Disorders	3 (3.7)	-	-	1 (1.8)	1 (1.2)

Body System / Adverse Event (preferred Term)	**Placebo N = 81**	**ACTEMRA 10 mg/kg (< 30 kg) N = 16**	**ACTEMRA 8 mg/kg (< 30 kg) N = 11**	**ACTEMRA 8 mg/kg (≥ 30 kg) N = 55**	**ACTEMRA All N = 82**
Oropharyngeal pain	2 (2.5)				
Respiratory tract irritation	1 (1.2)				
Tonsillar hypertrophy	1 (1.2)				
Cough				1 (1.8)	1 (1.2)
Skin and Subcutaneous Tissue Disorders	2 (2.5)	1 (6.3)	1 (9.1)	1 (1.8)	3 (3.7)
Alopecia	1 (1.2)				
Night sweats	1 (1.2)				
Ecchymosis		1 (6.3)			1 (1.2)
Eczema			1 (9.1)		1 (1.2)
Urticaria				1 (1.8)	1 (1.2)
Eye Disorders	2 (2.5)		-	-	-
Conjunctival haemorrhage	1 (1.2)				
Uveitis	1 (1.2)				
Injury, Poisoning and Procedural Complications	1 (1.2)	-	-	-	-
Excoriation	1 (1.2)				
Investigations	2 (2.5)	1 (6.3)	-	1 (1.8)	2 (2.4)
Liver function test abnormal	1 (1.2)				
Tuberculin test positive	1 (1.2)				
Blood bilirubin abnormal		1 (6.3)			1 (1.2)
Platelet count decreased				1 (1.8)	1 (1.2)
Nervous System Disorders	1 (1.2)	-	-	-	-
Dizziness	1 (1.2)				
Blood and Lymphatic System Disorders	1 (1.2)	-		-	-
Anaemia	1 (1.2)				
Ear and Labyrinth Disorders	1 (1.2)	-	-	-	-
Ear pain	1 (1.2)				
Reproductive System and Breast Disorders	1 (1.2)				
Pruritus general	1 (1.2)				
General and Administrative Site Disorders	-	1 (6.3)	1 (9.1)	-	2 (2.4)
Oedema			1 (9.1)		1 (1.2)
Pyrexia			1 (9.1)		1 (1.2)
Chest pain		1 (6.3)			1 (1.2)
Metabolism and Nutrition Disorders				2 (3.6)	2 (2.4)

Body System / Adverse Event (preferred Term)	Placebo N = 81	ACTEMRA 10 mg/kg (< 30 kg) N = 16	ACTEMRA 8 mg/kg (< 30 kg) N = 11	ACTEMRA 8 mg/kg (≥ 30 kg) N = 55	ACTEMRA All N = 82
Hyperlipidaemia				1 (1.8)	1 (1.2)
Hypertriglyceridaemia				1 (1.8)	1 (1.2)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)				1 (1.8)	1 (1.2)
Melanocytic naevus				1 (1.8)	1 (1.2)

Systemic Juvenile Idiopathic Arthritis

The safety of ACTEMRA in sJIA has been studied in 112 pediatric patients from 2 to 17 years of age. In the 12 week double-blind, controlled portion of the clinical trial 75 patients received treatment with ACTEMRA (8 mg/kg or 12 mg/kg, based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the on-going open-label extension phase.

Three of the 112 patients randomized, one in each treatment group, withdrew from treatment before the end of the 12 week double-blind period. The reasons for withdrawal included Serious Adverse Events (SAEs) in two patients and one patient who withdrew. At the time of this reporting, four additional patients withdrew for safety reasons during the open-label extension phase for an incidence of 3.6 % or rate 3.0 per 100 patient years.

In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see ADVERSE REACTIONS for RA section above).

Table 7 below lists the adverse events (judged to be at least remotely causally-related to treatment) occurring in ≥ 1% of patients treated with ACTEMRA during the initial 12 week double-blind controlled portion of the sJIA clinical trial.

Table 7: Adverse Events (judged to be at least remotely-causally related to treatment) Occurring in ≥1% of Patients Treated with ACTEMRA Dosed Every 2 Weeks During the Initial 12 Week Trial Period

Body System / Adverse Event (preferred Term)	Placebo* N = 37	ACTEMRA* 8 mg/kg N = 37	ACTEMRA 12 mg/kg N = 38	ACTEMRA All N = 75
Infections and Infestations	3	5	5	10
Upper Respiratory Tract Infection	2 (5.4)		1 (2.6)	1 (1.3)
Gastroenteritis Viral			1 (2.6)	1 (1.3)
Arthritis Bacterial		1 (2.7)		1 (1.3)
Candidiasis		1 (2.7)		1 (1.3)
Oral Herpes		1 (2.7)		1 (1.3)
Pharyngitis			1 (2.6)	1 (1.3)

Body System / Adverse Event (preferred Term)	**Placebo*** **N = 37**	**ACTEMRA* 8 mg/kg N = 37**	**ACTEMRA 12 mg/kg N = 38**	**ACTEMRA All N = 75**
Herpes Simplex	1 (2.7)			
Pneumonia Mycoplasmal			1 (2.6)	1 (1.3)
Rhinitis			1 (2.6)	1 (1.3)
Tonsillitis		1 (2.7)		1 (1.3)
Urinary Tract Infection		1 (2.7)		1 (1.3)
General Disorders and Administration Site Conditions	1	1	0	1
Asthenia		1 (2.7)		1 (1.3)
Fatigue	1 (2.7)			
Musculoskeletal and Connective Tissue Disorders	0	0	1	1
Juvenile Arthritis			1 (2.6)	1 (1.3)
Eye Disorders	0	1	0	1
Conjunctivitis		1 (2.7)		1 (1.3)
Metabolism and Nutrition Disorders	0	1	0	1
Decreased Appetite		1 (2.7)		1 (1.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	1	1
Skin Papilloma			1 (2.6)	1 (1.3)
Nervous System Disorders	2	3	0	3
Headache	1 (2.7)	2 (5.4)		2 (2.7)
Dizziness	1 (2.7)			
Somnolence		1 (2.7)		1 (1.3)
Psychiatric Disorders	0	0	1	1
Abnormal Behaviour			1 (2.6)	1 (1.3)
Reproductive System and Breast Disorders	0	0	1	1
Epididymitis			1 (2.6)	1 (1.3)
Respiratory, Thoracic and Mediastinal Disorders	4	1	0	1
Asthma	1 (2.7)			
Cough	1 (2.7)			
Oropharyngeal Pain	1 (2.7)	1 (2.7)		1 (1.3)
Pleuritic Pain	1 (2.7)			
Gastrointestinal Disorders	0	2	3	5
Abdominal Pain			1 (2.6)	1 (1.3)
Diarrhoea		1 (2.7)	1 (2.6)	2 (2.7)
Gastrointestinal Disorder		1 (2.7)		1 (1.3)
Vomiting			1 (2.6)	1 (1.3)
Blood and Lymphatic System	0	2	1	3

Body System / Adverse Event (preferred Term)	**Placebo*** **N = 37**	**ACTEMRA* 8 mg/kg N = 37**	**ACTEMRA 12 mg/kg N = 38**	**ACTEMRA All N = 75**
Disorders				
Lymphadenopathy		1 (2.7)		1 (1.3)
Neutropenia		1 (2.7)	1 (2.6)	2 (2.7)
Skin and Subcutaneous Tissue Disorders	0	1	7	8
Urticaria			3 (7.9)	3 (4.0)
Angioedema			1 (2.6)	1 (1.3)
Dermatitis Contact			1 (2.6)	1 (1.3)
Rash		1 (2.7)	1 (2.6)	2 (2.7)
Rash Pruritic			1 (2.6)	1 (1.3)
Investigations	0	2	1	3
Alanine Aminotransferase Increased		1 (2.7)		1 (1.3)
Neutrophil Count Decreased			1 (2.6)	1 (1.3)
Transaminases Increased		1 (2.7)		1 (1.3)
Renal and Urinary Disorders	2	0	0	0
Haematuria	1 (2.7)			
Nephrolithiasis	1 (2.7)			
Hepatobiliary Disorders	1	0	0	0
Hypertransaminasaemia	1 (2.7)			

*****20 patients receiving placebo and 1 patient receiving ACTEMRA 8 mg/kg escaped prior to week 12.

During the open label portion of the study the majority of AEs were mild (668 AEs in 108 patients (96.4%)) or moderate (221 AEs in 75 patients (67.0%)) in intensity. There were 5 new (not previously reported) severe AEs (single cases of otitis media at 12 mg/kg, and herpes zoster, osteoporosis, headache, testicular torsion at 8 mg/kg) for a total of 20 severe AEs (13.4%).

At the time of reporting, 29 patients receiving ACTEMRA (25.9%) reported 38 SAEs and the rate of the SAEs was 24.8 per 100 patient-years. The majority of SAEs each occurred in individual patients with the exception of varicella reported in 4 patients (12 mg/kg), gastroenteritis (8 and 12 mg/kg), pneumonia (12 mg/kg), histiocytosis haematophagic (MAS) (8 and 12 mg/kg) each reported in 3 patients, and herpes zoster (8 and 12 mg/kg), reported in 2 patients. Other SAEs reported in individual patients included pulmonary veno-occlusive disease (8 mg/kg), suspected pneumothorax (8 mg/kg) and cardiac failure (8 mg/kg). The incidence (31.1% vs. 23.1%) and rate (29.5 vs. 22.6 per 100 patient years) of the SAEs were higher in patients receiving ACTEMRA 12 mg/kg than in those receiving ACTEMRA 8 mg/kg, the difference being largely due to a higher incidence of infection SAEs (16.4and 8.0 events per 100 patient years, respectively).

The safety data from the 12 week controlled trial are supplemented by supportive trials conducted in Japan. A total of 149 patients with sJIA were included in these studies. A total of 2 patients died in these studies, 1 of MAS (see WARNINGS AND PRECAUTIONS, Macrophage Activation Syndrome (MAS)). The second death was in a 22 year old male patient, who died of

arrhythmia secondary to his cardiac amyloidosis 8 days following the 7th ACTEMRA dose administration. SAEs included (but were not limited to): GI haemorrhage, anaphylactoid symptoms and duodenal perforation. All of these patients received 8 mg/kg every 2 weeks.

Infections
In the 12 week controlled trial, there were 13 infections in 11 patients, 3 of which were judged to be at least causally related to treatment, reported in the placebo group (37 patients). In the ACTEMTRA groups, 17 infections in 14 patients, 5 of which were judged to be at least causally related to treatment, were reported in the 8 mg/kg treatment group (37 patients) and 29 infections in 20 patients, 5 of which were judged to be at least causally related to treatment, including one case of mycoplasmal pneumonia, were reported in the 12 mg/kg treatment group (38 patients). The increase in incidence in the 12 mg/kg group was mostly driven by upper respiratory tract infections, nasopharyngitis, gastroenteritis, and a number of different individual events.

In the 12 week controlled trial the rate of all infections in the all ACTEMRA group was 344.7 per 100 patient-years (247.3 per 100 patient-years: 8 mg/kg group; 437.6 per 100 patient-years: 12 mg/kg group and 287.0 per 100 patient-years in the placebo group. In the on-going open label extension study (Part II) the overall rate of infections was 303.6 per 100 patient-years (212.4 per 100 patient-years for 8 mg/kg and 422.8 per 100 patient-years for 12 mg/kg).

In the 12 week controlled trial, the rate of serious infections in the ACTEMRA group was 11.5 per 100 patient years (11.8 per 100 patient-years: 8 mg/kg group; 11.2 per 100 patient-years: 12 mg/kg group). There were 2 serious infections in the ACTEMRA group, Bacterial Arthritis (caused by Group G beta streptococci) reported in the 8 mg/kg treatment group and varicella reported in the 12 mg/kg treatment group. In the on-going open label extension study, the overall rate of serious infections was 11.4 per 100 patient-years. Newly reported serious infections were in the 8 and 12 mg/kg dose groups: gastroenteritis (including campylobacter jejuni), pneumonia and herpes zoster; in the 8 mg/kg dose group: otitis media (including haemolytical streptococcus group A), bronchopneumonia, and pharyngotonsillitis and in the 12 mg/kg dose group: gastroenteritis viral and upper respiratory tract infection.

Infusion Reactions
For sJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled trial, 3 patients (4.0%) patients from the ACTEMRA group (1 patient receiving 8 mg/kg and 2 patients receiving 12 mg/kg) experienced events occurring during the 3rd and 4th infusion, one event in a patient receiving 12 mg/kg, (angioedema, during the 5th infusion) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the 12 week controlled trial experience, 12 patients (16%) in the ACTEMRA group (5 patients receiving 8 mg/kg and 7 patients receiving 12 mg/kg) and 2 patients (5.4%) in the placebo group experienced an event within 24 hours of infusion. In the ACTEMRA group, the events included, but not limited to rash, (after 1st infusion of 8 mg/kg), urticaria (after 3rd infusion of 12 mg/kg),

diarrhea (after the 1st infusion of 12 mg/kg for one patient and the 3rd infusion of 12 mg/kg for a second patient), epigastric discomfort (after the 3rd infusion of 12 mg/kg), arthralgia (after the 1st infusion of 8 mg/kg) and headache (after the 1st infusion of 8 mg/kg). One of these events (urticaria) was considered serious.

Clinically significant hypersensitivity reactions associated with ACTEMRA, and requiring treatment discontinuation, were reported in 1 out of 112 patients (<1%) treated with ACTEMRA during the controlled and open-label parts of the clinical trial (see above).

In the clinical trial for sJIA, patients were not premedicated for the prevention of infusion reactions, however, most patients were on concomitant corticosteroids as part of their background treatment at the initiation of ACTEMRA treatment.

Immunogenicity
All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a life threatening hypersensitivity reaction leading to withdrawal (patient receiving 12 mg/kg). The second patient was randomized to placebo but received 12 mg/kg escape therapy.

Abnormal Hematologic and Clinical Chemistry Findings

Hematology Abnormalities:

RHEUMATOID ARTHRITIS

Neutrophils
In the 6-month controlled clinical studies, decreases in neutrophil counts below 1×10^9 / L occurred in 1.8% and 3.4% of patients in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group (see Table 7). Approximately half of the instances of ANC < 1×10^9/L occurred within 8 weeks of starting therapy. Decreases below 0.5×10^9 / L were reported in 0.4% and 0.3% of patients in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group (see WARNINGS and PRECAUTIONS: Laboratory Abnormalities).

In study II through 12 months of treatment decreases in neutrophil counts below 1×10^9 / L occurred in 2.3% and 4.5% of patients in the 4 mg/kg and 8 mg/kg ACTEMRA plus MTX group, respectively, compared to 0.0% of patients in the placebo plus MTX group. Decreases in neutrophil counts below 0.5×10^9 / L occurred in 0.5% and 0.3% of patients in the 4 mg/kg and 8 mg/kg ACTEMRA plus MTX group, respectively, compared to 0.0% of patients in the placebo plus MTX group.

In the cumulative dataset up to Week 104, patients who received ACTEMRA had greater mean decreases in ANC compared with subjects who received placebo + MTX. This dose-dependent decline in mean ANC was also seen in patients who switched from ACTEMRA 4 to 8 mg/kg.

A higher proportion of subjects (4.2%, 22/532) treated with ACTEMRA 8 mg/kg + MTX developed Grade 3 ANC compared with any other ACTEMRA treatment cohort including those in the switch treatment groups (1.1-2.1%) and placebo + MTX (0.03%, 1/392); nine patients (6 receiving ACTEMRA 8 mg/kg and 3 on ACTEMRA 4 mg/kg) developed Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L). Additionally 2 patients on placebo had a grade 4 neutropenia.

In the all exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical studies.

Platelets
In the 6-month controlled clinical studies, decreases in platelet counts below $100 \times 10^3 / \mu L$ occurred in 1.3% and 1.7% of patients on 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD (see Table 8).

In study II through 12 months of treatment decreases in platelet counts below $100 \times 10^3 / \mu L$ occurred in 1.8% and 2.0% of patients on 4 mg/kg and 8 mg/kg ACTEMRA plus MTX, respectively, compared to 0.5% of patients on placebo plus MTX.

In the cumulative data up to week 104, eight patients in the ACTEMRA groups had Grade 2 thrombocytopenia, two patients experienced Grade 3 thrombocytopenia (≥ 25 to $< 50 \times 10^9$/L) and three patients experienced Grade 4 thrombocytopenia ($< 25 \times 10^9$/L) (all of which were single occurrences.

In the all exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6- month controlled clinical studies.

Table 8 Clinically significant changes in hematological laboratory values in the 6 month controlled period

Laboratory Parameter	**ACTEMRA 8 mg/kg Monotherapy** **N = 288** **n (%)**	**Methotrexate** **N = 284** **n (%)**	**ACTEMRA 4 mg/kg + DMARDs** **N = 774** **n (%)**	**ACTEMRA 8 mg/kg + DMARDs** **N = 1582** **n (%)**	**Placebo + DMARDs** **N = 1170** **n (%)**
Neutropenia					
Grade 3/4 ($<1x10^9$/L)	9 (3.1%)	1 (0.4%)	14 (1.8%)	54 (3.4%)	1 (0.1%)
Thrombocytopenia					
$<100 \times 10^3 / \mu L$	4 (1.4%)	1 (0.4%)	10 (1.3%)	27 (1.7%)	6 (0.5%)

Table 9 Clinically significant changes in hematological laboratory values through 12 months of treatment for Study II (Lithe)

Body System/ Adverse Event	Placebo + MTX* N=392 (%)	ACTEMRA (Plac→4) 4 mg/kg+ MTX N=196$^{\Delta}$ (%)	ACTEMRA (Plac→4→8) 8mg/kg + MTX N=30$^{\Delta}$ (%)	ACTEMRA (4 and 4→8) 4 mg/kg +MTX* N=399 (%)	ACTEMRA (4→8) 8 mg/kg+ MTX N=95$^{¥}$ (%)	ACTEMRA 8 mg/kg+ MTX* N=399 (%)

Body System/ Adverse Event	Placebo + MTX* N=392 (%)	ACTEMRA (Plac→4) 4 mg/kg+ MTX N=196$^{\Delta}$ (%)	ACTEMRA (Plac→4→8) 8mg/kg + MTX N=30$^{\Delta}$ (%)	ACTEMRA (4 and 4→8) 4 mg/kg +MTX* N=399 (%)	ACTEMRA (4→8) 8 mg/kg+ MTX N=95$^{¥}$ (%)	ACTEMRA 8 mg/kg+ MTX* N=399 (%)
Neutropenia						
Grade 3/4 (<1x10^{9}/L)	1(<1%)	1(<1%)	0	10 (2.5%)	3 (3.2%)	18 (4.5%)
Thrombocytopenia						
<100 x 10^{3} / μL	2(<1%)	1(<1%)	0	7 (1.8%)	1(1.1%)	8 (2.0%)

* These groups represent the original randomized treatment assignments.
Patients may be included in more than one treatment group because of the option for patients to received escape therapy.
$^{\Delta}$ *Represents patients who started on placebo+MTX escaped to ACTEMRA 4 mg/kg; this includes 30 patients who started on MTX+placebo, escaped to 4 mg/kg and then subsequently escaped to 8mg/kg ACTEMRA.*
$^{¥}$ *Includes 95 patients who started on 4 mg/kg escaped to 8 mg/kg ACTEMRA*

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Neutrophils
During routine laboratory monitoring in the ACTEMRA all exposure population, a decrease in neutrophil count below 1 × 10^{9}/L occurred in 3.2 % of patients [6 of 188, 1 patient in the 10 mg/kg (<30 kg) group, 3 patients in the 8 mg/kg (<30 kg) group and 2 patients in the 8 mg/kg (≥30 kg) group]. There was no clear relationship between decreases in neutrophils below 1 x 10^{9}/L and the occurrence of serious infections. No event of serious infection occurred among the 6 patients during the period of decrease neutrophil below 1 x 10^{9}/L. Two patients experienced infections (both non-serious) on the same day the neutropenia was reported (gastroenteritis, 8 mg/kg [≥30 kg]) and 3 days prior to the neutropenia (tracheitis, 10 mg/kg [<30kg]).

Platelets
During routine laboratory monitoring in the ACTEMRA all exposure population, 2% [4 of 188, 2 patients on 10 mg/kg (<30kg) and 2 patients on 8 mg/kg (≥30kg)] of patients had a decrease in platelet count to ≤100× 10^{3} / μL without associated bleeding events.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

Neutrophils
During routine laboratory monitoring in the 12 week controlled trial, a decrease in neutrophil counts below 1 × 10^{9}/L occurred in 7% of patients in the ACTEMRA group compared to no decrease for patients in the placebo group.

In the ongoing open-label extension study, decreases in neutrophil counts below 1 x 10^{9}/L occurred in 17% of the ACTEMRA group.

During the 12 week controlled trial, there were two non-serious infection adverse events (AE), in the same patient that occurred within 21 days of neutrophil counts being below 1×10^9 /L. The infections were infective conjunctivitis and a tooth abscess in a patient receiving 12 mg/kg.

During the open-label period there were two additional patients, at 12 mg/kg that had infectious AEs within 21 days of neutrophil counts being below 1×10^9 /L. The infection AEs were mild conjunctivitis, mild upper respiratory tract infection and mild nasopharyngitis.

Platelets
During routine laboratory monitoring in the 12 week controlled trial, 3% (1 of 37) of patients in the placebo group and 1% in the ACTEMRA group (1 patient randomized to 12 mg/kg) had a decrease in platelet count to $\leq 100 \times 10^3/\mu L$.

In the ongoing open-label extension study, decreases in platelet counts below 100 x 10^3 / μL occurred in 4% (4 patients on 8 mg/kg and 1 patient on 12 mg/kg) of patients of the ACTEMRA group, without associated bleeding events.

Liver Enzyme Elevations:

RHEUMATOID ARTHRITIS

In the 6-month controlled trials, transient elevations in ALT / AST > 3 x ULN were observed in 4.9% of patients on MTX compared to 2.1% of patients on ACTEMRA 8 mg/kg and in 5.9% and 6.5% of patients who received 4 mg/kg and 8 mg/kg ACTEMRA plus traditional DMARDs, respectively, compared to 1.5% of patients on placebo plus traditional DMARDs. The addition of potentially hepatotoxic drugs (e.g. MTX), to ACTEMRA monotherapy resulted in increased frequency of these elevations. Elevations of ALT / AST >5 x ULN were observed in 0.7% of ACTEMRA monotherapy patients and 1.4% of ACTEMRA plus traditional DMARD patients, the majority of whom were discontinued from ACTEMRA treatment. These elevations were not associated with any clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency. Increases in indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, were observed in 0% of patients on MTX compared to 4.5% of patients on ACTEMRA 8 mg/kg, and in 3.5% and 6.1% of patients who received 4 mg/kg and 8 mg/kg ACTEMRA plus traditional DMARDs, respectively, compared to 0.8% of patients on placebo plus traditional DMARDs.

In study II through 12 months of treatment elevations in ALT / AST > 3 x ULN were observed in 8.3% and 10.3% of patients who received 4 mg/kg and 8 mg/kg ACTEMRA plus MTX, respectively, compared to 1.8% of patients on placebo plus MTX. Increases in indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, were observed in 6.0% and 11.0% of patients who received 4 mg/kg and 8 mg/kg ACTEMRA plus MTX, respectively, compared to 1.3% of patients on placebo plus MTX.

Three hundred and ninety nine (399) patients whose only dose of ACTEMRA was 8 mg/kg (in year 1), increased from < 3x ULN at baseline to a worst post-baseline results > 3x ULN occurred

ALT: 10.3% (41/399) of patients in year 1 compared to 12.2% (65/532) in year 2; AST: 3% (12/399) of patients in year 1 compared to 4.3% (23/532) in year 2.

Four hundred and fifty one (451) patients who switched from ACTEMRA 4 mg/kg to 8 mg/kg (post switch), increased from <3x ULN at baseline to a worst post-baseline results > 3x ULN occurred in: ALT: 6.0% (27/451) vs. 8.5% (38/451) and AST: <1.0% (3/451) vs. 2.4% (11/451) by comparison pre vs. post switch.

In the all exposure population, the pattern and incidence of elevations in ALT/AST remained consistent with what was seen in the 6 month controlled clinical trials.

Table 10 Incidence of ALT/AST in the 6-Month Controlled Period

	ACTEMRA 8 mg/kg Monotherapy N = 288 n(%)	**Methotrexate N = 284 n(%)**	**ACTEMRA 4 mg/kg + DMARDs N = 774 n(%)**	**ACTEMRA 8 mg/kg + DMARDs N = 1582 n(%)**	**Placebo + DMARDs N = 1170 n(%)**
ALT (U/L)					
>ULN to 3x ULN	105(36)	95(33)	349(45)	763(48)	269(23)
> 3x ULN to 5x ULN	4(1.4)	11(3.9)	36(4.7)	80(5.1)	15(1.3)
> 5x ULN	2(0.7)	3(1.1)	10(1.3)	23(1.5)	3(0.3)
AST (U/L)					
>ULN to 3x ULN	64(22)	74(26)	264(34)	646(41)	194(17)
> 3x ULN to 5x ULN	1(0.3)	5(1.8)	8(1.0)	29(1.8)	3(0.3)
> 5x ULN	2(0.7)	1(0.4)	1(0.1)	3(0.2)	1(< 0.1)

ULN = Upper Limit of Normal

Table 11 Incidence of ALT/AST through 12 months of treatment for Study II (Lithe)

Body System/ Adverse Event	Placebo + MTX* N=392(%)	ACTEMRA (Plac→4) 4 mg/kg+ MTX N=196[Δ] (%)	ACTEMRA (Plac→4→8) 8mg/kg + MTX N=30[Δ] (%)	ACTEMRA (4 and 4→8) 4 mg/kg +MTX* N=399 (%)	ACTEMRA (4→8) 8 mg/kg+ MTX N=95[¥] (%)	ACTEMRA 8 mg/kg+ MTX* N=399 (%)
ALT (U/L)						
>ULN to 3x ULN	114 (29)	82 (42)	10 (33)	208 (52)	45 (47)	240 (60)
> 3x ULN to 5x ULN	6 (2)	9 (5)	0 (0)	23 (6)	3 (3)	32 (8)
> 5x ULN	1(<1)	3 (2)	0 (0)	10 (2.5)	3 (3)	12 (3)
AST (U/L)						
>ULN to 3x ULN	85 (22)	55 (28)	6 (20)	168 (42)	34 (36)	219 (55)
> 3x ULN to 5x ULN	1 (<1)	2 (1)	0 (0)	7 (2)	2 (2)	13 (3)
> 5x ULN	0 (0)	2 (1)	0 (0)	2 (<1)	0 (0)	0 (0)

* These groups represent the original randomized treatment assignments.
ULN = Upper Limit of Normal

Patients may be included in more than one treatment group because of the option for patients to received escape therapy.

[Δ] *Represents patients who started on placebo+MTX escaped to ACTEMRA 4 mg/kg; this includes 30 patients who started on MTX+placebo, escaped to 4 mg/kg and then subsequently escaped to 8mg/kg ACTEMRA.*

[¥] *Includes 95 patients who started on 4 mg/kg escaped to 8 mg/kg ACTEMRA*

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

During routine laboratory monitoring in the ACTEMRA all exposure population, elevation in ALT or AST ≥3 x ULN occurred in 3.7% [1 patient in the 10 mg/kg (<30 kg) group and 6 patients in the 8 mg/kg (≥30 kg) group] and <1% [1 patient in the 8 mg/kg (≥30 kg) group] of patients, respectively.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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

In the ongoing open-label extension study, elevation in ALT or AST ≥ 3 x ULN occurred in 13% and 5% of patients, respectively, in the ACTEMRA group.

Elevations in Lipid Parameters:

RHEUMATOID ARTHRITIS

During routine laboratory monitoring, the 6-month controlled trials, elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed 6 weeks following initiation of ACTEMRA and remained stable thereafter. Increases in triglycerides to levels above 5.64 mmol/L were observed. Approximately 24% of patients receiving ACTEMRA in clinical trials experienced sustained elevations in total cholesterol > 6.2 mmol/L, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L.

Changes in lipid parameters from baseline to week 24 were evaluated and are summarized below:

- Mean LDL increased by 0.34 mmol/L in the ACTEMRA 4 mg/kg+DMARD arm, 0.52 mmol/L in the ACTEMRA 8 mg/kg+DMARD, and 0.65 mmol/L in ACTEMRA 8 mg/kg monotherapy.
- Mean HDL increased by 0.08 mmol/L in the ACTEMRA 4 mg/kg+DMARD arm, 0.13 mmol/L in the ACTEMRA 8 mg/kg+DMARD, and 0.10 mmol/L in ACTEMRA 8 mg/kg monotherapy.
- Mean LDL/HDL ratio increased by an average of 0.12 in the ACTEMRA 4 mg/kg+ DMARD arm, 0.16 in the ACTEMRA 8 mg/kg+DMARD, and 0.31 in ACTEMRA 8 mg/kg monotherapy.

In the majority of patients there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid-lowering agents.

In study II through 12 months of treatment elevations in total cholesterol > 6.2 mmol/L were observed in 21.8% and 36.1% of patients who received 4 mg/kg and 8 mg/kg ACTEMRA plus MTX, respectively, compared to 18.4% of patients on placebo plus MTX. Elevations in LDL to ≥ 4.1 mmol/L were observed in 16.0% and 23.8% of patients who received 4 mg/kg and 8 mg/kg ACTEMRA plus MTX, respectively, compared to 11.2% of patients on placebo plus MTX. Changes in lipid parameters from baseline to week 52 were evaluated and are summarized below:

- Mean LDL increased by 0.36 mmol/L in the ACTEMRA 4 mg/kg + MTX arm, 0.53 mmol/L in the ACTEMRA 8 mg/kg + MTX, and 0.09 mmol/L in the placebo plus MTX arm.
- Mean HDL increased by 0.07 mmol/L in the ACTEMRA 4 mg/kg + MTX arm, 0.09 mmol/L in the ACTEMRA 8 mg/kg + MTX, and 0.04 mmol/L in the placebo plus MTX arm.
- Mean LDL/HDL ratio increased by an average of 0.18 in the ACTEMRA 4 mg/kg + MTX arm, 0.23 in the ACTEMRA 8 mg/kg + MTX, and 0.02 in the placebo plus MTX arm.

During initial randomized treatment up to 12 months, based on ATPIII thresholds, increases in LDL-cholesterol from < 4.1 mmol/L at baseline to ≥ 4.1 mmol/L at last observation (excluding patients with missing values) were more frequent in the ACTEMRA + MTX groups (ACTEMRA 4 mg/kg + MTX 14%, ACTEMRA 8 mg/kg + MTX 18%) than in the placebo + MTX group (4%). A similar trend was observed for shifts in total cholesterol, HDL-cholesterol and triglycerides.

In the all exposure population, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6 month controlled clinical trials. Based on categorical analysis of the LDL by ATPIII guidelines showed that 29.2% of patients had an LDL ≥ 3.4 mmol/L at baseline. This percentage increased by 20.9 percentage points at week 24 (to 50.1%) and by 26.1 percentage points at week 176 (to 55.3%).

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

During routine laboratory monitoring in the ACTEMRA all exposure population, elevation in total cholesterol >1.5x ULN to 2x ULN occurred in one patient (0.5%) and elevation in LDL >1.5x ULN to 2x ULN in one patient (0.5%). Both of these occurred in patients in the 8 mg/kg (≥ 30 kg) group.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

During routine laboratory monitoring in the 12 week controlled trial, elevation in total cholesterol >1.5 x ULN to 2 x ULN occurred in 1.5% of the ACTEMRA group and in 0% of placebo patients. Elevation in LDL >1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the ACTEMRA group and 0% of the placebo group.

In the ongoing open-label extension study, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled trial data.

Post-Market Adverse Drug Reactions

Additional adverse events have been identified during post-marketing use of ACTEMRA. Because these events 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 ACTEMRA exposure.

The safety profile in post marketing experience is consistent with clinical trial data. Very rare reports of pancytopenia have occurred in the post marketing setting. Globally, serious hypersensitivity reactions related to ACTEMRA have been reported uncommonly.

The postmarketing experience with events of anaphylaxis has been consistent with the clinical trial experience with the exception of post-market reports of fatal anaphylaxis (see WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions).

In the post-marketing experience, of patients reported to have neutropenia, 13/90 (14%) were also reported to have serious infections within 30 days of having neutropenia.

In a Japanese post marketing surveillance study the incidence of serious infection-related ADRs in pJIA patients was 3.35%, with eight events (8.54 /100 PY) reported. The serious infection-related ADRs were enteritis infectious (1.12%) and cellulitis, mumps, pneumonia mycoplasmal, pyelonephritis and septic shock (each 0.56%). The septic shock and enteritis infectious occurred in the same patient. The overall incidence of infection-related ADRs was higher in patients with steroid use (22.79%) than in those without steroid use at the start of ACTEMRA treatment (9.30%). Additionally the incidence of infection ADRs was 25% (2/8 patients) for patients with white blood cell counts of $<4 \times 10^9$/L and 19.05% (32/168 patients) for white blood cell counts of $>4 \times 10^9$/L. The analysis of lymphocyte counts showed that the incidence of infection ADRs was 23.81% (5/21 patients) for lymphocyte counts of $<1 \times 10^9$/L and 18.92% (28/148 patients) for lymphocyte counts of $>1 \times 10^9$/L. The analysis of neutrophil counts showed that the incidence of infection ADRs was 19.16% (32/167 patients) for neutrophil counts of $>1 \times 10^9$/L. No infection ADRs occurred in patients with neutrophil counts $<1 \times 10^9$/L.

DRUG INTERACTIONS

Drug-Drug Interactions

Population pharmacokinetic analyses did not detect any effect of methotrexate, non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance. Concomitant administration of a single dose of 10 mg/kg ACTEMRA with 10-25 mg methotrexate once weekly had no clinically significant effect on methotrexate exposure.

ACTEMRA has not been studied in combination with other biological DMARDs.

Treatment with ACTEMRA in combination with azathioprine, cyclophosphamide, or chlorambucil is limited or has not been studied, therefore the benefits and risks of such combinations are unknown.

Interactions with CYP450 Substrates: The expression of hepatic CYP450 enzymes is suppressed by the pro-inflammatory cytokines such as IL-6. Thus, it is expected that for any drug with a potent anti-cytokine inhibition such as ACTEMRA, CYP450 suppression may be reversed when introduced in patients with rheumatoid arthritis.

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).

When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given the elimination half-life ($t_{1/2=}$13 days), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

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/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/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/kg), dextromethorphan exposure was decreased by approximately 5%. However, a larger decrease (29%) in dextrorphan levels was noted after ACTEMRA infusion.

DOSAGE AND ADMINISTRATION

RHEUMATOID ARTHRITIS

Dosing Considerations

- It would be prudent not to use ACTEMRA in patients who are using azathioprine or cyclophosphamide
- ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists.
- Treatment with biological DMARDs such as TNF inhibitors has been associated with reactivation of Hepatitis B and C. Therefore screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ACTEMRA. In clinical studies with ACTEMRA, patients who screened positive for hepatitis were excluded from the study
- ACTEMRA treatment should be interrupted if a patient develops a serious infection until the infection is controlled.
- Continuing therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Recommended Dose and Dosage Adjustment

Recommended Dose
ACTEMRA should be given in combination with methotrexate (MTX) or other DMARDs. ACTEMRA may also be given as monotherapy in cases of intolerance to MTX or where treatment with MTX is not appropriate. The recommended dose of ACTEMRA for adult patients with rheumatoid arthritis given once every 4 weeks as an intravenous infusion over 1 hour is:

Recommended Adult Dosage Every 4 Weeks	
Patients who have had an inadequate response to one or more DMARDs and/or TNF antagonists	**When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response**

In clinical trials with ACTEMRA, patients with the following laboratory parameter were not initiated: Platelet count < 100,000/mm^3, hemoglobin (Hb) < 8.5 g/dL, WBC < 3000/mm^3, ANC < 2.0 x 10^9/L, absolute lymphocyte count < 500/mm^3, ALT or AST > 1.5 x upper limit of normal (ULN), total bilirubin > ULN, Triglycerides (TG) > 10 mmol/L (> 900 mg/dL), Serum creatinine > 1.4 mg/dL in female patients and > 1.6 mg/dL in male patients.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see DETAILED PHARMACOLOGY: Clinical Pharmacokinetics of tocilizumab).

Dose Adjustments

The following dose adjustments are recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

Liver enzyme abnormalities

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until ALT/AST have normalized
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt tocilizumab dosing until < 3x ULN and follow recommendations above for > 1 to 3x ULN For persistent increases > 3x ULN, discontinue tocilizumab
> 5x ULN	Discontinue tocilizumab

Low absolute neutrophil count (ANC)

Lab Value (cells x 10^9/l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt tocilizumab dosing When ANC > 1 x 10^9/l resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue tocilizumab

Low platelet count

Lab Value (cells x $10^3/\mu l$)	Action

50 to 100	Interrupt tocilizumab dosing When platelet count is > 100 x $10^3/\mu l$ resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue tocilizumab

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS (PJIA)

Recommended Dose

The recommended dose of ACTEMRA for patients with pJIA is:

- 10 mg/kg for patients < 30 kilograms (kgs),
- 8 mg/kg for patients ≥ 30 kilograms (kgs),

given in combination MTX, once every four weeks as an IV infusion. A change in dose should only be based on a consistent change in the patient's body weight over time. ACTEMRA may also be given as monotherapy in cases of intolerance to MTX or where treatment with MTX is not appropriate.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

Recommended Dose

ACTEMRA can be used alone or in combination with MTX. The recommended dose of ACTEMRA for patients with sJIA given once every two weeks as an IV infusion over 1 hour is:

- 8 mg/kg for patients ≥ 30 kilograms (kgs),
- 12 mg/kg for patients < 30 kilograms (kgs).

A change in dose should only be based on a consistent change in the patient's body weight over time.

Dose Adjustments for pJIA and sJIA

Dose reduction of ACTEMRA has not been studied in the pJIA or sJIA population. Dose interruptions of ACTEMRA for laboratory abnormalities are recommended in patients with pJIA or sJIA and are similar to what is outlined above for patients with RA (see WARNINGS AND PRECAUTIONS, Laboratory Abnormalities). If appropriate, concomitant methotrexate and/or other medications should be dose modified or interrupted and ACTEMRA dosing interrupted until the clinical situation has been evaluated. In pJIA or sJIA the decision to discontinue ACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Special Dosage Instructions

Pediatric: The safety and efficacy of ACTEMRA in children with conditions other than pJIA or sJIA have not been established. Children under the age of two have not been studied.

Geriatric: As with all biologics, there is a higher incidence of infections in the elderly population in general, therefore, caution should be used when treating the elderly.

Renal impairment: No dose adjustment is required in patients with mild renal impairment (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions/ Renal Insufficiency). ACTEMRA has not been studied in patients with moderate to severe renal impairment.

Hepatic impairment: The safety and efficacy of ACTEMRA has not been studied in patients with hepatic impairment (see WARNINGS AND PRECAUTIONS: Active Hepatic Disease and Hepatic Impairment). Therefore, no dose recommendations can be made.

Administration

RHEUMATOID ARTHRITIS:

ACTEMRA concentrate for intravenous infusion should be diluted to 100 mL by a healthcare professional using aseptic technique as follows:

- Withdraw the required amount of ACTEMRA for a dose of 4 mg/kg or 8 mg/kg (equivalent to 0.2 mL/kg or 0.4 mL/kg, respectively).
- Withdraw the same amount of sterile, non-pyrogenic 0.9% w/v sodium chloride solution from the infusion bag and discard.
- Slowly add the withdrawn ACTEMRA concentrate into the infusion bag. **The final volume in the infusion bag should total 100 mL.**
- To mix the solution, gently invert the bag to avoid foaming.
- 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.**

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS (PJIA) AND SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

- ACTEMRA concentrate for intravenous infusion should be diluted by a healthcare professional using aseptic technique as outlined below.

pJIA and sJIA Patients ≥ 30 kg:

- Withdraw the required amount of ACTEMRA for a dose of 8 mg/kg (equivalent to 0.4 mL/kg).
- From a 100 mL infusion bag, withdraw the same amount of sterile, non-pyrogenic 0.9% w/v sodium chloride solution from the infusion bag and discard.
- Slowly add the withdrawn ACTEMRA concentrate into the infusion bag. **The final volume in the infusion bag should total 100 mL.**

pJIA Patients < 30 kg:

- Withdraw the required amount of ACTEMRA for a dose of 10 mg/kg (equivalent to 0.5 mL/kg).
- From a 50 mL infusion bag, withdraw the same amount of sterile, non-pyrogenic 0.9% w/v sodium chloride solution from the infusion bag and discard.
- Slowly add the withdrawn ACTEMRA concentrate into the infusion bag. **The final volume in the infusion bag should total 50 mL.**

sJIA Patients < 30 kg:

- Withdraw the required amount of ACTEMRA for a dose of 12 mg/kg (equivalent to 0.6 mL/kg).
- From a 50 mL infusion bag, withdraw the same amount of sterile, non-pyrogenic 0.9% w/v sodium chloride solution from the infusion bag and discard.
- Slowly add the withdrawn ACTEMRA concentrate into the infusion bag. **The final volume in the infusion bag should total 50 mL.**

For all pJIA and sJIA Patients:

- To mix the solution, gently invert the bag to avoid foaming.
- 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.**

For All Prepared Infusion Solutions: ACTEMRA does not contain preservatives, therefore reconstitution and dilution of the product should be performed under aseptic conditions. The prepared infusion solution of tocilizumab is physically and chemically stable in 0.9% w/v sodium chloride solution at 2ºC – 8ºC or 30ºC for 24 hours. From a microbiological point of view, the prepared infusion should be used immediately (see STORAGE AND STABILITY).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ACTEMRA is a colorless to pale yellow liquid. 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.

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.

OVERDOSAGE

There are limited data available on overdosage with ACTEMRA (tocilizumab). One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions

were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose-limiting neutropenia was observed.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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 sIL-6R and mIL-6R-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 the most abundantly produced cytokine by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis

Pharmacodynamics

RHEUMATOID ARTHRITIS

In clinical studies of ACTEMRA (tocilizumab), decreases in levels of C-reactive protein (CRP) to within normal ranges were seen as early as week 2 and were maintained while on treatment. Decreases in rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA) were also observed in the clinical studies. Improvements in hemoglobin were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to the nadir 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see WARNINGS and PRECAUTIONS, Laboratory Abnormalities: Neutrophils).

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/kg single dose in RA patients, mean CL was 0.29±0.10 ml/hr/kg and mean apparent terminal t1/2 was 151±59 hours (6.3 days).

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1793 rheumatoid arthritis patients treated with tocilizumab 4 and 8 mg/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/kg every 4 weeks. Maximum concentration (C_{max}) increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 2.7 and 6.5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively. In a long-term study with dosing for two years, observed C_{min} was sustained over time.

The following parameters are valid for a dose of 4 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800·µg·hr/mL, 1.49 ± 2.13 µg/mL, and 88.3 ± 41.4µg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 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 for Cmin.

The following parameters are valid for a dose of 8 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 µg·hr/mL, 9.74 ± 10.5 µg/mL, and 183 ± 85.6 µg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Tocilizumab AUC, Cmin and Cmax increased with increase of body weight. At body weight > 100 kg, the predicted mean (± SD) steady state AUC, Cmin and Cmax of tocilizumab were 55500 ± 14100 mcg·hr/mL, 19.0±12.0 mcg/mL, and 269±57 mcg/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

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

Excretion: The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in rheumatoid arthritis patients. 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 in rheumatoid arthritis, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and up to 13 days for 8 mg/kg every 4 weeks in patients with RA at steady state.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with systemic juvenile idiopathic arthritis treated with 8 mg/kg (patients with a body weight $\geq$ 30 kg) or 12 mg/kg (patients with a body weight $<$ 30 kg), given every 2 weeks. At 8 mg/kg (body weight $\geq$ 30kg), the predicted mean ($\pm$ SD) AUC_{2weeks}, and observed C_{max} and C_{min} of tocilizumab were 32087 $\pm$ 9814 µg·hr/mL, 257 $\pm$75 µg/mL and 69 $\pm$ 25 µg/mL, respectively. The accumulation ratio for the observed C_{min} (week12/week2) was 3.2 $\pm$ 1.4. At 12mg/kg (body weight $<$ 30 kg), the predicted mean ($\pm$ SD) AUC_{2weeks}, and observed C_{max} and C_{min} of tocilizumab were 32294 $\pm$ 10213 µg·hr/mL, 279 $\pm$79 µg/mL and 71 $\pm$ 31 µg/mL, respectively. The accumulation ratio for the observed C_{min} (week12/week2) was 3.2 $\pm$ 1.2. The tocilizumab C_{min} was stabilized after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

Distribution: In pediatric patients with sJIA, the central volume of distribution was 35 ml/kg and the peripheral volume of distribution was 60 ml/kg resulting in a volume of distribution at steady state of 95 ml/kg.

Excretion: The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 7.1 mL/h in pediatric patients with systemic juvenile idiopathic arthritis.

The $t_{1/2}$ of tocilizumab in children with sJIA at steady state ranged from 18.4 to 22.7 days at 8 mg/kg for body weight $\geq$ 30 kg and ranged from 19.2 to 23 days at 12 mg/kg for body weight $<$ 30 kg.

Special Populations and Conditions

Pediatrics: ACTEMRA is not recommended for use in children below 2 years of age due to a lack of data on safety and efficacy.

Hepatic Insufficiency: No formal study of the effect of hepatic impairment on the pharmacokinetics of ACTEMRA was conducted.

Renal Insufficiency: No formal study of the effect of renal impairment on the pharmacokinetics of ACTEMRA was conducted.

Most of the patients in the rheumatoid arthritis population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault $<$ 80 mL/min and $\geq$ 50 mL/min) did not impact the pharmacokinetics of ACTEMRA.

Other Special Populations: Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of ACTEMRA in adult rheumatoid arthritis patients. Results of these analyses showed that no adjustment of the dose is necessary for age, gender, or race.

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/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.

STORAGE AND STABILITY

ACTEMRA (tocilizumab) vials should be stored in a refrigerator at 2 to 8°C. Do not freeze. Keep the vial in the outer carton to protect it from light. Do not use beyond expiration date stated on the vial and carton.

For prepared infusion solution: ACTEMRA does not contain preservatives, therefore reconstitution and dilution of the product should be performed under aseptic conditions. The prepared infusion solution of tocilizumab is physically and chemically stable in 0.9% w/v sodium chloride solution at 2ºC – 8ºC or 30ºC for 24 hours. From a microbiological point of view, the prepared infusion should be used immediately.

ACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.

SPECIAL HANDLING INSTRUCTIONS

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established 'collection systems' if available in your location.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

- Type I glass single use vial with a stopper (butyl rubber) containing 80 mg of tocilizumab in 4 ml (20 mg/ml). Packs of 1 and 4 vials.

- Type I glass single use vial with a stopper (butyl rubber) containing 200 mg of tocilizumab in 10 ml (20 mg/ml). Packs of 1 and 4 vials.

- Type I glass single use vial with a stopper (butyl rubber) containing 400 mg of tocilizumab in 20 ml (20 mg/ml). Packs of 1 and 4 vials.

* Not all pack sizes may be marketed.

Listing of Non-Medicinal Ingredients

In addition to the active ingredient tocilizumab, each ACTEMRA vial contains the following non-medicinal ingredients: disodium phosphate dodecahydrate, polysorbate 80, sodium dihydrogen phosphate dihydrate, sucrose, and water for injections.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

ACTEMRA (tocilizumab) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. The tocilizumab molecule is composed of two heterodimers, and each of the heterodimers is composed of a heavy (H) and a light (L) polypeptide chain. 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 protein solution for intravenous (IV) infusion at a concentration of 20 mg/mL. ACTEMRA is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Injectable solutions of ACTEMRA are formulated in an aqueous solution containing sucrose (50 mg/mL), polysorbate 80 (0.5 mg/mL), and disodium phosphate dodecahydrate and sodium dihydrogen phosphate dihydrate (as a 15 mmol/L phosphate buffer).

CLINICAL TRIALS

RHEUMATOID ARTHRITIS

Study Demographics and Trial Design

The efficacy and safety of ACTEMRA was assessed in five randomized, double-blind, multicenter studies in patients > 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). The primary endpoint in all 5 studies was the proportion of patients who achieved an ACR20 response at week 24.

Table 12 Summary of Patient Demographics for Clinical Trials in Rheumatoid Arthritis (ITT populations)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (SD)	Gender (% Female)	Mean Baseline Disease Duration (years)
Study I (AMBITION)[5]	Multi-center, randomized,	ACTEMRA 8mg/kg IV every 4 weeks for	286	51 (13)	83	6.4
MTX-Naïve	double-blind, double-dummy, parallel group, placebo controlled multiple dose	24 weeks. MTX (escalating dose from 7.5 - 20 mg/week over 8 week period) for 24 weeks	284 99	50 (13)	79	6.2

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (SD)	Gender (% Female)	Mean Baseline Disease Duration (years)
	monotherapy study	(Placebo/ACTEMRA 8 mg/kg substudy)				
Study II (LITHE) Inadequate Response to MTX	Multi-center, double-blind, randomized, placebo controlled multiple dose study combined with MTX Double-blinded for one year, and open-label for the second year	ACTEMRA 4mg/kg + MTX ACTEMRA 8mg/kg + MTX Placebo + MTX ACTEMRA administered intravenously every 4 weeks for 24 months.	399 398 393	51 (13) 53 (12) 51 (12)	84 82 83	9.4 9.3 8.9
Study III (OPTION)[6] Inadequate Response to MTX	Multi-center, double-blind, randomized, placebo controlled multiple dose study combined with MTX	ACTEMRA 4mg/kg + MTX ACTEMRA 8mg/kg + MTX Placebo + MTX ACTEMRA administered intravenously every 4 weeks for 24 weeks.	213 205 204	51 (13) 51 (12) 51 (12)	82 85 78	7.4 7.5 7.8
Study IV (TOWARD)[7] Inadequate Response to DMARD	Multi-center, double-blind, randomized, placebo controlled multiple dose study combined with DMARDs	ACTEMRA 8mg/kg + DMARD Placebo + DMARD ACTEMRA administered intravenously every 4 weeks for 24 weeks.	803 413	53 (13) 54 (13)	81 84	9.8 9.8
Study V (RADIATE)[8] Inadequate Response to TNF Antagonist	Multi-center, double-blind, randomized, placebo controlled multiple dose study combined with MTX	ACTEMRA 4mg/kg + MTX ACTEMRA 8mg/kg + MTX Placebo + MTX ACTEMRA administered intravenously every 4 weeks for 24 weeks.	161 170 158	51 (12) 54 (13) 53 (13)	81 84 79	11.0 12.6 11.4

Description of Clinical Studies

In Study I, ACTEMRA was administered intravenously every four weeks as monotherapy. In Studies II, III and V, ACTEMRA was administered intravenously every four weeks in combination with MTX vs. placebo and MTX. In Study IV, ACTEMRA was administered intravenously every 4 weeks in combination with other traditional DMARDs vs. placebo and other traditional DMARDs.

Study I (AMBITION)[5] evaluated 673 patients who had not been treated with MTX within 6 months prior to randomization, and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX naïve. Doses of 8 mg/kg of ACTEMRA were given every four weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 to a maximum of 20 mg weekly over an 8 week period).

Study II (LITHE was a 2 year study with an ongoing optional 3-year extension phase with two planned interim analyses at week 24 and week 52 that evaluated 1196 patients with moderate to severe rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg/kg, ACTEMRA 4 mg/kg, or placebo every four weeks, in combination with MTX (10 - 25 mg weekly). Upon completion of 52-weeks, patients received open-label treatment with ACTEMRA 8 mg/kg through 104-weeks or they had the option to continue their double-blind treatment if they maintained a >70% improvement in swollen/tender joint count. The primary endpoint at week 24 was the proportion of patients who achieved an ACR20 response. At weeks-52 and 104 the co-primary endpoints were change from baseline in modified total Sharp-Genant score and change in physical function as measured by the AUC of the change from baseline in HAQ-DI score.

Study III (OPTION)[6] evaluated 623 patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg/kg, ACTEMRA 4 mg/kg, or placebo every four weeks, in combination with MTX (10 – 25 mg weekly).

Study IV (TOWARD)[7] evaluated 1220 patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received ACTEMRA 8 mg/kg or placebo every four weeks, in combination with the stable DMARDs.

Study V (RADIATE)[8] evaluated 499 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/kg, ACTEMRA 4 mg/kg, or placebo every four weeks, in combination with MTX (10 – 25 mg weekly).

Study Results

ACR Response

The percent of patients achieving ACR 20, 50 and 70 responses in Studies I to V are shown in Table 13. In all studies, patients treated with 8 mg/kg ACTEMRA had statistically superior ACR20, ACR50, and ACR70 response rates versus MTX- or placebo-treated patients ($p<0.01$) at week 24.

Patients treated with ACTEMRA at a dose of 4 mg/kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with ACTEMRA 8 mg/kg.

Table 13 ACR Response at 6 Months in Active and Placebo Controlled Trials (Percent of Patients)

Percent of Patients												
	Study I (AMBITION)		Study II (LITHE)			Study III (OPTION)			Study IV (TOWARD)		Study V (RADIATE)		
Response Rate Week 24	MTX N=284	ACTEMRA 8 mg/kg N=286	Placebo + MTX N=393	ACTEMRA 4 mg/kg + MTX N=399	ACTEMRA 8 mg/kg + MTX N=398	Placebo + MTX N=204	ACTEMRA 4 mg/kg + MTX N=213	ACTEMRA 8 mg/kg + MTX N=205	Placebo + DMARDs N=413	ACTEMRA 8 mg/kg + DMARDs N=803	Placebo + MTX N=158	ACTEMRA 4 mg/kg + MTX N=161	ACTEMRA 8 mg/kg + MTX N=170
ACR20													
Responders	53%	70%***	27%	51%	56%***	27%	48%	59%***	25%	61%***	10%	30%***	50%***
Weighted Difference %[a] (95% CI)[b]		19 (11, 27)		23 (17, 29)	29 (23, 35)		23 (15, 32)	32 (23, 41)		35 (30, 40)		25 (15, 36)	46 (36, 56)
ACR50													
Responders	34%	44%**	10%	25%	32%***	11%	32%	44%***	9%	38%***	4%	17%	29%***
Weighted Difference %[a] (95% CI)[b]		12 (4, 20)		15 (9, 20)	22 (16, 28)		21 (13, 29)	33 (25, 41)		28 (23, 33)		15 (5, 25)	31 (21, 41)
ACR70													
Responders	15%	28%**	2%	11%	13%***	2%	12%	22%***	3%	21%***	1%	5%	12%**
Weighted Difference %[a] (95% CI)[b]		14 (7, 22)		8 (3, 13)	10 (5, 15)		11 (4, 18)	20 (12, 27)		17 (13, 21)		4 (-6, 13)	12 (3, 22)

[a] The weighted difference is the difference between ACTEMRA and Placebo response rates, adjusted for site (and disease duration for Study I only).
[b] CI: 95% confidence interval of the weighted difference
** *p<0.01, ACTEMRA vs. placebo+MTX/Traditional DMARDs*
*** *p<0.0001, ACTEMRA vs. placebo+MTX/Traditional DMARDs*

The results of the components of the ACR response criteria for Studies III and V are shown in Table 14. Similar results to Study III were observed in Studies I, II and IV.

Table 14 Components of ACR Response at 6 Months

	Study III (OPTION)						Study V (RADIATE)					
	ACTEMRA 4 mg/kg + MTX N=213		ACTEMRA 8 mg/kg + MTX N=205		Placebo + MTX N=204		ACTEMRA 4 mg/kg + MTX N=161		ACTEMRA 8 mg/kg + MTX N=170		Placebo + MTX N=158	
Component (mean)	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**
Number of tender joints (0-68)	33	19 -7.0 (-10.0, -4.1)	32	14.5 -9.6 (-12.6, -6.7)	33	25	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
Number of swollen joints (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
Pain[b]	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
Patient global assessment[b]	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45	70	46 -10.0 (-20.3, 0.3)	70	36 -17.4 (-27.8, -7.0)	71	51
Physician global assessment[b]	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
Disability index (HAQ)[c]	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg/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

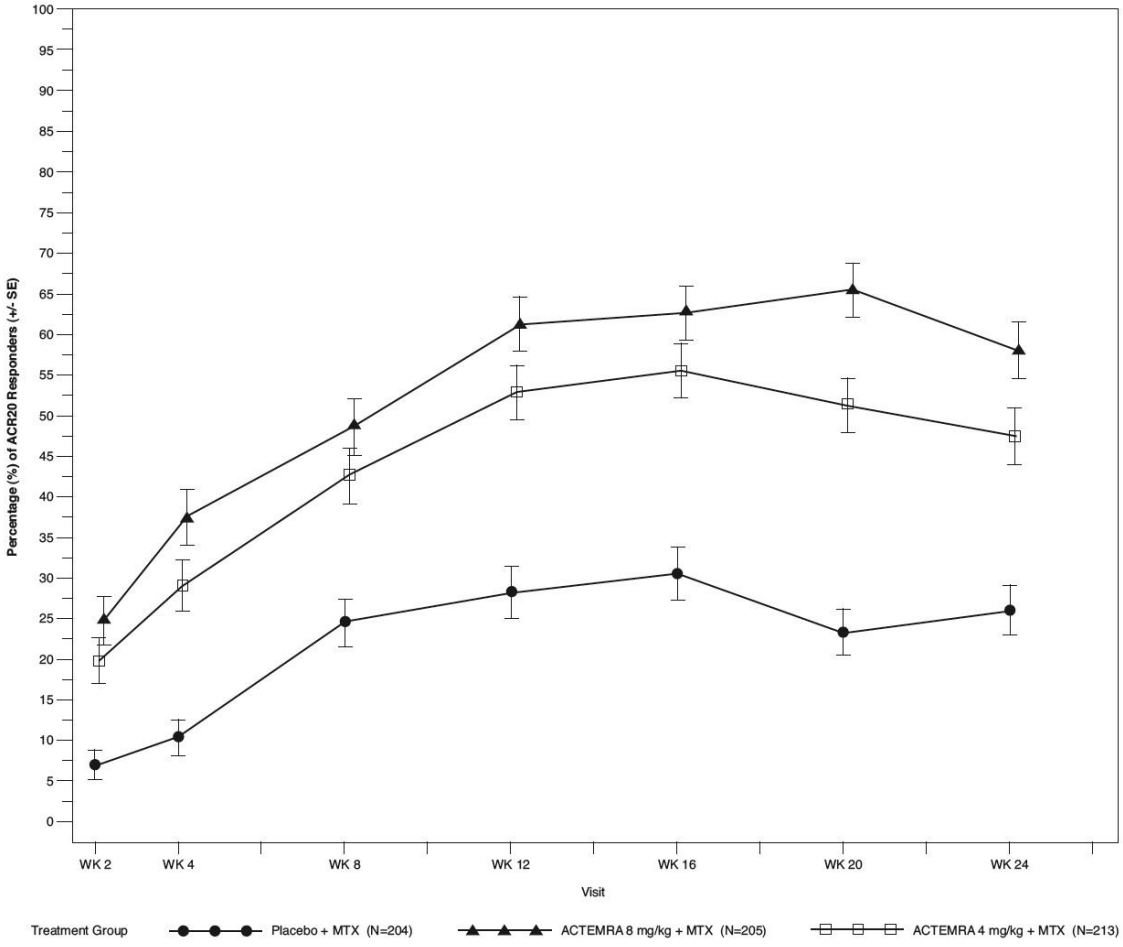
[b] Visual analog scale: 0 = best, 100 = worst

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

ACR Response Rates over Time

The percent of ACR20 responders by visit for Study III is shown in Figure 1. Similar increases in responses over time were observed in studies I, II, IV, and V.

Figure 1: Percent of ACR20 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, i.e., 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 15.

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 8mg per kg groups was 0.34 (SD = 1.24). By 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% (193/294) of patients experienced no radiographic progression (Total Sharp-Genant Score change ≤ 0) at week 52 compared to 78%(268/343) and 83% (294/353) in the ACTEMRA 4 mg per kg and 8 mg per kg, respectively.

Table 15 Radiographic mean changes at 52 weeks in Study II

	Placebo +MTX (+option of ACTEMRA from week 16) N= 393 Mean	ACTEMRA 4 mg/kg + MTX (+option of ACTEMRA to 8 mg/kg from 16 weeks) N = 399 Mean	ACTEMRA 8 mg/kg + MTX N = 398 Mean
Changes from baseline to Week 52			
n	290	339	348
Total Sharp-Genant score, Mean (SD)	1.13 (2.96)	0.34 (1.45)	0.29 (1.28)
Adjusted Mean Difference * (97.5% CI)**		-0.77 (-1.12, -0.41)	-0.81 (-1.16, -0.46)
Erosion score , Mean (SD)	0.71 (1.89)	0.21 (0.92)	0.17 (0.86)
JSN score, Mean (SD)	0.42 (1.70)	0.13 (0.74)	0.12 (0.64)

MTX - Methotrexate
JSN - Joint space narrowing
** Difference between the adjusted means (Actemra + MTX - Placebo + MTX). The means are adjusted for region.*
SD = standard deviation
*** The 97.5% confidence intervals are displayed as a significance level of 0.025 was used to test the co-primary endpoint*
All data presented was read together in campaign 1 which consists of the evaluations of the baseline, week 24, week 52 and early withdrawal or escape therapy readings taken up to week 52 visit

Monotherapy: ACTEMRA versus HUMIRA

Study WA19924 (ADACTA) evaluated 326 patients with moderate to severe RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the ACTEMRA arm received an intravenous (IV) infusion of ACTEMRA (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the HUMIRA arm received a HUMIRA SC injection (40 mg) q2w plus an IV placebo infusion q4w).

A statistically significant difference was seen in the primary endpoint (DAS28 change from baseline to week 24) and the week 24 ACR20/50/70 scores with ACTEMRA (8mg/kg) (q4w) vs. HUMIRA (40mg) (q2w).

Table 16: Efficacy Results for Study WA 19924

	HUMIRA 40 mg + Placebo (IV) N = 162	ACTEMRA 8 mg/kg + Placebo (SC) N = 163	p-value[(a)]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean) (95% CI)	**-1.8** ***(-2.10, -1.55)***	**-3.3** ***(-3.57, -3.02)***	
Difference in adjusted mean (95% CI)	**-1.5 (-1.8, -1.1)**		**<0.0001**
Secondary Endpoints - Percentage of Responders at Week 24[(b)]			
ACR20 response, n (%)	80 (49.4)	106 (65.0)	
ACR50 response, n (%)	45 (27.8)	77 (47.2)	
ACR70 response, n (%)	29 (17.9)	53 (32.5)	

[a] *p* value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.
[b] Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

For the safety summary in study WA19924 see ADVERSE REACTIONS, Monotherapy: ACTEMRA versus HUMIRA.

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Study Demographics and Trial Design

The efficacy of ACTEMRA was assessed in a three-part study including an open-label extension in children with active polyarticular juvenile idiopathic arthritis (pJIA) which was defined as 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 number of active joints 20.3; limited movement 17.6). 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 (ITT, n=163). The primary endpoint was the proportion of patients with a JIA ACR30 flare at week 40 vs. 16, defined as 3 or more of the 6 core variables worsened by at least 30% with no more than 1 of the remaining variables improved by >30 %).

Patients ≥ 30 kg received ACTEMRA at 8 mg/kg for 4 doses. Patients < 30 kg were randomized 1:1 to receive either ACTEMRA 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline entered the blinded withdrawal period (Part II; 82 in the ACTEMRA group, 84 in the placebo group) of the study. These responders (n=163, Intent to Treat Population) were randomized to ACTEMRA (same dose received in Part I) or placebo in a 1:1 ratio 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 ACR30 flare criteria (relative to Week 16) and qualified for escape.

Study Results

At the conclusion of Part I, JIA ACR 30/50/70 responses were 89.4%, 83.0% and 62.2%. Responses by dose/weight are summarized below:

Table 17 JIA ACR Response Rates at Week 16

	ACTEMRA 10 mg/kg (< 30 kg) N = 35 No. (%)	**ACTEMRA 8 mg/kg (< 30 kg) N = 34 No. (%)**	**ACTEMRA 8 mg/kg (≥ 30 kg) N = 119 No. (%)**	**ACTEMRA All N = 188 No. (%)**
JIA ACR 30	31 (88.6)	26 (76.5)	111 (93.3)	168 (89.4)
JIA ACR 50	28 (80.0)	24 (70.6)	104 (87.4)	156 (83.0)
JIA ACR 70	22 (62.9)	14 (41.2)	81 (68.1)	117 (62.2)

Across all groups, approximately 79% of patients were taking concomitant MTX, 65% were taking NSAIDs, and 50% were taking corticosteroids.

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.

Forty eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of ACTEMRA-treated patients. These proportions were statistically significantly different (p=0.0024). Table 18 below provides number of patients with flare at week 40 by treatment group.

Table 18 Part II: Number of Patients with Flare at Week 40 by Treatment Group

	10 mg/kg (< 30 kg)	**8 mg/kg (< 30 kg)**	**8 mg/kg (≥30 kg)**	**All**
Placebo N	15	13	53	81
Flare N (%)	8 (53.3)	5 (38.5)	26 (49.1)	39 (48.1)
ACTEMRA N	16	11	55	82
Flare N (%)	3 (18.8)	2 (18.2)	16 (29.1)	21 (25.6)

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

Study Demographics and Trial Design

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 (either 8 mg/kg for patients ≥30 kg or 12 mg/kg for patients < 30 kg), and 37 patients were assigned to receive placebo infusions every two weeks. The randomization stratification factors include body weight, disease duration, background corticosteroid dose, and background methotrexate use. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape (due to disease worsening) patients were treated in the open-label extension phase at weight appropriate dosing.

Patients aged 2-16 received 12 mg/kg (mean 6.6 years) and patients aged 7-17 received 8 mg/kg (mean 13.5 years). Placebo patients ranged in age from 2-17 (mean 9.1 years).

Three of the 112 patients randomized, one in each treatment group, withdrew from treatment before the end of the 12-week randomized, double blind, placebo-controlled period of the study. The reasons for withdrawal included an SAE of MAS in a patient randomized to placebo, after escape to 12 mg/kg of ACTEMRA, an SAE of angioedema in a patient randomized to 12 mg/kg and withdrawal of consent in a patient randomized to 8 mg/kg.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30 response) at Week 12 and absence of fever (no temperature recording ≥ 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 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).

Study Results

Eighty five percent (64/75) of the patients treated with ACTEMRA and 24.3% (9/37) of placebo patients achieved the primary endpoint of at least 30% improvement in JIA ACR core set at Week 12 and absence of fever. These proportions were significantly different ($p<0.0001$) (See Table 19).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in the table below. In the open-label extension, through 48 weeks of treatment 82.1 % (78 of 95 patients) achieved the primary endpoint of JIA ACR30 response with absence of fever.

Table 19 Response Rates at Week 12

Response Rate Week 12	ACTEMRA N=75	Placebo N=37
Primary Endpoint: JIA ACR 30 + absence of fever		
Responders	85.3%	24.3%
Weighted difference (95% CI)[b]	61.5* (44.9, 78.1)	-
JIA ACR Response Rates at Week 12		
JIA ACR 30		
Responders	90.7%*	24.3%
Weighted difference[a] (95% CI)[b]	66.8 (50.7, 82.9)	-
JIA ACR 50		
Responders	85.3%*	10.8%
Weighted difference[a] (95% CI)[b]	74.0 (57.9, 90.1)	-
JIA ACR 70		
Responders	70.7%*	8.1%
Weighted difference[a] (95% CI)[b]	62.9 (46.1, 79.7)	-
JIA ACR 90		
Responders	37.3%*	5.4%
Weighted difference[a] (95% CI)[b]	33.3 (16.8, 49.7)	-

** $p<0.0001$, tocilizumab vs. placebo*

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

[b] CI: confidence interval of the weighted difference.

To control for the rate of false positive conclusions, a fixed sequence approach was applied to secondary endpoints. Testing was carried out based on pre-specified hierarchical ordering, hence no adjustment for multiplicity was required.

Systemic Features

In those patients treated with ACTEMRA, 35 out of 41 (85%) who had fever due to sJIA at baseline were free of fever (no temperature recording $\geq 37.5°C$ in the preceding 14 days) at week 12 versus 5 out of 24 (21%) of placebo patients and 14 out of 22 (64%) of ACTEMRA treated patients with rash characteristic of sJIA at baseline were free of rash at week 12 versus 2 out of 18 (11%) of placebo patients**.**

In the open-label extension, at 48 weeks of treatment 11 (17.7%) out of 62 patients (who had fever at baseline) had fever present and 24 (61.5%) out of 39 patients (who had a rash at baseline) had rash present (based on assessment in last 14 days.

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 ACR70 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 ACR30 flare or occurrence of systemic symptoms to week 12. Reductions in corticosteroids continued, with 44 out of 91 (48%) ACTEMRA patients off oral corticosteroids, at week 44, while maintaining ACR responses.

Quality of Life
Physical function and disability were assessed using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Seventy-seven percent (77%, 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.

Laboratory Parameters
Fifty out of seventy five (67%) patients treated with ACTEMRA had a hemoglobin < LLN at baseline. Forty (80%) of these patients with decreased hemoglobin had an increase in their hemoglobin to within the normal range at week 12, in comparison to 2 out of 29 (7%) of placebo patients with hemoglobin < LLN at baseline.

The proportion of patients with thrombocytosis at baseline who had a normal platelet count at week 12 was 90% (47 out of 52) in the ACTEMRA treatment group and 4% (1 out of 26) in the placebo treatment group.

DETAILED PHARMACOLOGY

Clinical Pharmacokinetics of Tocilizumab

RHEUMATOID ARTHRITIS

The pharmacokinetics of tocilizumab are best described by a two compartment disposition model with parallel first order (linear or concentration-independent clearance) and Michaelis Menten elimination (non linear or concentration dependent clearance) kinetics. Therefore, the total clearance of tocilizumab is the sum of the nonlinear and linear clearances.

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 linear. This pattern is consistent with a specific and saturable antigen mediated clearance at lower exposures and a non specific linear clearance mediated by the reticuloendothelial system at higher tocilizumab exposures, the latter representing the same route of elimination as for other IgG antibodies. An apparent half-life of about 21 days is obtained if the contribution of non linear clearance is assumed to be negligible at high tocilizumab concentrations. This value is similar to that known for other human IgG antibodies (ie, 23 days).

The possibility of the non linear clearance being antigen-mediated is supported by *in vitro* data on the mechanism of action of tocilizumab. For example, values for the dissociation constant (KD) vary from 0.1 to 0.4 μg/mL. Maximum inhibition of IL 6 binding to sIL 6R occurs at approximately 4 μg/mL, and maximum inhibition of IL 6/sIL 6R signaling occurs at 1 μg/mL. These values are in the range of the value obtained for the Michaelis-Menten constant (ie, 2.7 μg/mL) in RA patients.

As a consequence of the non linear clearance, the PK characteristics of tocilizumab are concentration- and dose dependent at low exposures.

The volume of distribution of the central compartment of tocilizumab was 3.5 L, which approximates the serum volume and is in the range of what has been previously described for IgGs and other monoclonal antibodies. The volume of distribution at steady state (Vss) (6.4 L) tends to indicate a limited distribution into the body. However, it is known that, for most antibodies, distribution into tissues is often part of the elimination process and not part of the distribution process and hence contributes to the small apparent distribution volumes. Thus, a small Vss should not necessarily be interpreted as low tissue penetration and adequate concentrations may be reached in a single target organ due to receptor mediated uptake.

The PK parameters of tocilizumab did not change with time. Accumulation ratios for the area under the concentration time curve (AUC) and the maximum concentration (C_{max}) were low, while the highest ratios were observed for trough concentration (C_{min}): 1.96 and 2.35 for tocilizumab 4 and 8 mg/kg, respectively. This is expected based on the contribution of non linear clearance at low tocilizumab concentrations. For the 4 mg/kg and 8 mg/kg doses, steady state was achieved for C_{max}, AUC and C_{min} following the first administration, after 4 to 8 weeks and after 16 to 20 weeks, respectively. The inter-subject variability for tocilizumab was moderate (44%, 47%, and 107% for AUC, C_{max} and C_{min}, respectively, at steady state for tocilizumab 8 mg/kg every 4 weeks).

Age, gender, race and ethnicity had no impact on the PK of tocilizumab. Body size (body surface area, body weight, body mass index [BMI]) had an effect on clearance; this was accounted for by body weight adjusted dosing, although this adjustment results in slightly higher exposures to tocilizumab with higher body weight. This did not affect efficacy or safety parameters in a clinically relevant manner, thus indicating that body weight based dose regimens are appropriate for clinical practice. Mild renal impairment did not alter the PK of tocilizumab.

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.

The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight $\geq$ 30 kg) given every 4 weeks. The predicted mean ($\pm$ SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 29500 $\pm$ 8660 μg·hr/mL, 182 $\pm$ 37 μg/mL and 7.49 $\pm$ 8.2 μg/mL, respectively.

The following parameters are valid for a dose of 10 mg/kg tocilizumab (patients with a body weight < 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 23200 ± 6100 µg.hr/mL, 175 ± 32 µg/mL and 2.35 ± 3.59 µg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{min} for 10 mg/kg (BW < 30 kg) and 8 mg/kg (BW ≥ 30 kg) doses, respectively. No accumulation for C_{max} was observed (1.01 and 1.04 for 10 mg/kg (BW < 30 kg) and 8 mg/kg (BW ≥ 30 kg) doses, respectively).

Distribution: 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 predicted volume of distribution at steady state of 4.08 L.

Excretion: The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 5.8 mL/h in pediatric patients with pJIA.

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 ≥ 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady state.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with systemic juvenile idiopathic arthritis treated with 8 mg/kg (patients with a body weight ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg), given every 2 weeks. At 8 mg/kg (body weight ≥ 30kg), the predicted mean (± SD) AUC_{2weeks}, and observed C_{max} and C_{min} of tocilizumab were 32087 ± 9814 µg.hr/mL, 257 ±75 µg/mL and 69 ± 25 µg/mL, respectively. The accumulation ratio for the observed C_{min} (week12/week2) was 3.2 ± 1.4. At 12mg/kg (body weight < 30 kg), the predicted mean (± SD) AUC_{2weeks}, and observed C_{max} and C_{min} of tocilizumab were 32294 ± 10213 µg.hr/mL, 279 ±79 µg/mL and 71 ± 31 µg/mL, respectively. The accumulation ratio for the observed C_{min} (week12/week2) was 3.2 ± 1.2. The tocilizumab C_{min} was stabilized after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

In sJIA patients, the central volume of distribution was 35 ml/kg and the peripheral volume of distribution was 60 ml/kg resulting in a volume of distribution at a steady state of 95 ml/kg. The $t_{1/2}$ of tocilizumab in children with sJIA at steady state ranged from 18.4 to 22.7 days at 8 mg/kg for body weight ≥ 30 kg and ranged from 19.2 to 23 days at 12 mg/kg for body weight < 30 kg.

Clinical Pharmacodynamics

RHEUMATOID ARTHRITIS

C reactive protein (CRP) is synthesized by hepatocytes as a direct effect of IL 6 stimulation. Elevated CRP levels are an indication of the intensity of inflammation in RA and CRP is

included in the assessment of response using the ACR criteria. A dose dependent decrease in CRP was observed in RA patients at tocilizumab doses of 4 mg/kg and 8 mg/kg. For the tocilizumab 8 mg/kg every 4 weeks schedule, CRP levels were markedly suppressed as early as week 2 in the majority of patients (over 90%) and sustained around the normal range during the entire dosing interval, indicating persistent and consistent suppression of the joint degrading inflammation associated with RA synovitis. Only slight fluctuations in CRP were observed in a few patients following this dose. Sustained decreases in ESR were also observed in most patients.

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Seventy-eight (of 188) patients had an elevated CRP concentration (>10 mg/L) at baseline. The concentration had normalized 2 weeks after their first dose of tocilizumab in the majority of these patients (76/78 [97.4%]). The proportion of patients with normalized CRP at 16 weeks was lower in the <30 kg group receiving the lower dose (8 mg/kg) of tocilizumab (63.2%, 12/19) than the > 30 kg group (87%, 40/46) or than those receiving the higher dose (10 mg/kg) of tocilizumab (76.9%, 10/13). The clinical relevance of CRP normalization in this population has yet to be determined.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

CRP
Following administration of tocilizumab, a rapid decline in mean CRP was observed in the tocilizumab treatment groups. Of those patients with an elevated CRP at Baseline, 71 (98.6%) tocilizumab patients and two (5.9%) placebo patients had a CRP ≤ Upper Limit of Normal (ULN) at Week 12. Mean and median CRP values decreased over time from 166.4 mg/L ± 349.3 and 107.7 mg/L at Baseline to 3.2 ± 24.6 mg/L and 0.1 mg/L at Week 48, with further decreases up to Week 72.

Hemoglobin
Of those patients with anemia at Baseline, 40 (80.0%) tocilizumab patients and two (6.9%) placebo patients had Hb ≥ lower limit of normal at Week 12. The difference in proportions was statistically significant ($p<0.0001$). It was found that the proportion of patients with normalized Hb levels, which had increased from 30.4% at Baseline to 83.0% at Week 12, was maintained through Week 72 (92.6%).

TOXICOLOGY

Carcinogenicity
No long-term animal studies have been performed to establish the carcinogenicity potential of ACTEMRA (tocilizumab). However, pre-clinical studies conducted with tocilizumab or MR16-1 demonstrated anti-proliferative effects. Tocilizumab inhibited the proliferation of IL-6 dependent cell lines such as the human myeloma cell line *in vitro* and *in vivo*. Likewise, MR16-1 prevented the lympho-proliferative manifestations in an IL-6 transgenic mouse model of Castleman's Disease and stopped the progression of tumour growth in a mouse model of colon carcinoma. In

addition, proliferate lesions have not been observed in a chronic monkey 6-month toxicity study nor were they described in knock-out mice under chronic IL-6 depletion.

Mutagenicity
Standard genotoxicity studies with tocilizumab in both prokaryotic and eukaryotic cells were all negative.

Impairment of Fertility
Preclinical data do not suggest an effect on fertility under treatment with an analogue of tocilizumab. Effects on endocrine active organs or on organs of the reproductive system were not seen in a chronic cynomolgus monkey toxicity study, nor were the reproductive performance affected in IL-6 deficient mice. *In vitro* tissue cross reactivity studies conducted in both human and cynomolgus tissues did not show any binding specificity to organs involved in reproduction.

Teratogenicity
When tocilizumab was administered intravenously to cynomolgus monkeys during early gestation, no direct or indirect harmful effects on embryo-fetal development were observed.

Animal Toxicology and/or Pharmacology
A study in cynomolgus monkeys demonstrated plasma-exposure correlated binding of tocilizumab to neutrophils. There is no apparent correlation between tocilizumab binding to neutrophils and functional deficits, such as chemotaxis or neutrophil phagocyte activity. A transient reduction in absolute neutrophil counts was seen in monkeys following repeated daily IV administration (up to 50 mg/kg/day) over 28 days without associated changes in differential counts or effects on the bone marrow compartment.

An embryonal/fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Animals were administered tocilizumab via the IV route during early gestation (organogenesis period; post-coitum days 20 through 50) with doses of 2, 10 or 50 mg/kg/day. The exposures in monkeys from a 50 mg/kg/day dose were > 100 times the exposures in humans from an 8 mg/kg dose, administered every 4 weeks (based on C_{trough}). In this study there was an increase in the incidence of abortion/embryo-fetal death in the 10 and 50 mg/kg/day high-dose groups, i.e., incidence rates were 10%, 10%, 20% and 30% for the control, 2, 10 and 50 mg/kg groups, respectively. The abortions at 50 mg/kg bw (body weight) were considered to be treatment-related and it was considered equivocal whether the abortions at 10 mg/kg bw were related to treatment.

Testing of a murine analogue of tocilizumab, i.e. MR16-1, in responder mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation 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. At the tested dose levels there was maximal pharmacological effectiveness of the murine analogue and high embryonal exposure to the murine analogue of tocilizumab.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

Table 20: Summary of Toxicology Studies

Study Type	Treatment Duration	Species/ Test system	Animals/ group	Dose (mg/kg/day)	Results
General toxicity					
Single-dose IV	1 day (+ 14 days recovery)	Rat (Sprague Dawley) (6 weeks-old)	5 M 5 F	0, 6, 30, 150	During the 14-day observation period there were no deaths in any group and no obvious signs of toxicity were noted in general condition or body weight profile. Pathological examination at Day 14 post-administration did not find any abnormality and no anti-TCZ antibodies were detected. LD_{50} > 150 mg/kg
Single-dose IV	1 day (+ 8 weeks recovery)	Monkey (cynomolgus) (2.5-4 years old)	1 M 1 F	0, 1, 10, 100	During the 8-week observation period, there were no deaths in any group and no obvious signs of toxicity due to the drug were noted in general condition, body-weight profile and hematological or biochemical examination. Anti-TCZ antibodies were detected in the males in the 1 and 10 mg/kg groups from 2 weeks following injection through to the end of the observation period. LD_{50} > 100 mg/kg
Repeated-dose IV once-daily	28 days (+ 4 weeks recovery)	Rat (Sprague Dawley) (6 weeks-old)	15 M 15 F	0, 2, 10, 50	There were no consistent patterns of change in hematology, urinalysis or blood biochemistry investigations and no autopsy findings to suggest toxicity. Anti-TCZ antibodies were detected in one male in the 2 mg/kg group. During the recovery phase anti-TCZ antibodies were detected in 1 male and 4 females in the 2 mg/kg group, 2 males and 1 female in the 10 mg/kg group and 1 male and 1 female in the 50 mg/kg group. The toxicological no-effect dose in the rat was determined to be 10 mg/kg (in the 50 mg/kg group body-weight suppression and decrease in food and water consumption were observed in the females).
Repeated-dose IV once-daily	2 weeks	Monkey (cynomolgus) (2.5-4.0 years old)	2 M 2 F	0.4, 2, 10, 50	There were no TCZ-related toxic changes noted in the general condition, body weight, urinalysis, blood examination, bone marrow examination, or pathological examination even at the high dose of 50 mg/kg/day. Anti-TCZ antibodies were detected in 2 males and 2 females treated with the minimal dose of 0.4 mg/kg of TCZ and in 1 male and 1 female treated with 2 mg/kg of TCZ. Anti-TCZ antibodies were not detected in any animals in the 10 mg/kg or 50 mg/kg groups. The toxicological no-effect dose in the monkey was determined to be 50 mg/kg
Repeated-dose IV once-daily	1 month (+ 4 weeks recovery)	Monkey (cynomolgus) (3-4 years old)	4 M 4 F	0, 2, 10, 50	No obvious signs of toxicity due to TCZ were noted. A slight decrease in neutrophil counts in the 50 mg/kg group did not reverse on cessation of the drug. An increase in the γ-globulin fraction ratio was observed in the 50 mg/kg group. Anti-TCZ antibody was detected in 3 out of 4 males and 2 out of 4 females in the 2 mg/kg group, and in one male and one female in the 10 mg/kg group. Anti-TCZ antibodies not detected in any animals in the 50 mg/kg group. During the recovery period anti-TCZ antibody-positive cases became negative and no new positive cases were recorded. Toxicological no-effect dose determined to be 10 mg/kg (decreased neutrophil counts observed in the 50 mg/kg group). The toxicological no-effect dose in the monkey was determined to be 100 mg/kg
Repeated-dose IV once-weekly	6 months (+ 8 weeks recovery)	Monkey (cynomolgus) (2-4 years old)	4 or 5M 4 or 5F	0, 1, 10, 100 (weekly dose)	Repeated administration of 100 mg/kg/week of TCZ to cynomolgus monkeys for 6 months did not induce any toxic changes related to treatment.

Table 20: Summary of Toxicology Studies (Cont.)

Study Type	Treatment Duration	Species/ Test system	Animals/ group	Dose (mg/kg/day)	Results
General toxicity					
Repeat dose sc once weekly	9 weeks (+ 16 weeks recovery	Monkey (cynomolgus) (3-4 years old)	5M/5F	0, 100 mg/kg	Repeated subcutaneous administration of 100 mg/kg/week of TCZ to cynomolgus monkeys for 6 months did not induce any toxic changes related to treatment. There was no evidence for anti-TCZ-antibody formation.
Repeat dose sc once weekly	13 weeks (+ 16 weeks recovery)	Monkey (cynomolgus) (3-8 years old)	5M/5F	0, 100 mg/kg	Repeated administration of 100 mg/kg/week of TCZ in combination with recombinant human hyaloronidase (rHuPH20) to cynomolgus monkeys for 13 weeks did not yield evidence for any local or systemic toxic changes related to treatment. Antibodies developed towards rHuP20 did not have any influence on the exposure to TCZ
Genotoxicity					
Ames test	*in vitro*	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and *Escherichia coli* (WP2*uvr*A)		47.3 –757 µg/plate	No genotoxic activity.
Chromosomal aberration test	*in vitro*	Human lymphocytes		189-757 µg/mL	No genotoxic activity.
Reproductive toxicology					
Fertility & implantation IV	Males: once-daily from 28 days prior to mating, total 43 days. Females: once-daily from 14 days prior to mating to Day 7 of gestation	Rat (Sprague Dawley) (M: 8 weeks-old; F: 9 weeks-old)	18 M 18 F	0, 5, 16, 50	No abnormalities observed at autopsy in the estrous cycle, mating potency, fertility, spermatogenesis, embryo implantation rate or post-implantation viability. Normal rate of estrous cycle was reduced significantly to 50% in the 5 mg/kg group. This effect was not observed in higher dose groups, suggesting that this was not related to administration of TCZ. Although some changes were seen in males administered more than 5 mg/kg daily (slight decreases in hemoglobin and hematocrit; no abnormalities were noted in their reproductive functioning). The toxicological no-effect dose for reproductive functions in the male and female and early embryogenesis is 50 mg/kg daily.
Embryo-fetal development IV	Once-daily from Day 7 to 17 of gestation	Rat (Sprague Dawley) (females: 12-13 weeks-old)	19-20 F	0, 5, 16, 50	No changes in the general condition, body-weight, food consumption, and autopsy findings. On examination by Caesarean section, the number of corpora lutea, number of implantations, implantation rate, number of live fetuses and fetal viability were not affected by TCZ. No effects of TCZ were observed in the fetuses with respect to fetal weight, sex ratio and frequency of visceral or skeletal anomalies, frequency of skeletal variations or number of ossified sacral and caudal vertebrae. In addition, no external anomalies were noted. The toxicological no-effect dose for maternal toxicity, embryo/fetal toxicity and developmental toxicity is 50 mg/kg.

Table 20: Summary of Toxicology Studies (Cont.)

Study Type	Treatment Duration	Species/ Test system	Animals/ group	Dose (mg/kg/day)	Results
Reproductive toxicology (cont.)					
Embryo-fetal development IV	Once-daily from Day 6 to 18 of gestation	Rabbit (Japanese White) (4-6 months-old)	16-20 F	0, 0.5, 5, 50	No effect of TCZ on general condition. Rabbits given 5 mg/kg TCZ showed a decrease in body-weight gain on Day 22 to 28, and food consumption on Day 17 to 20 of gestation. In these rabbits, an increase in fetal mortality was observed as well as a decrease in fetal body weight. The number of corpora lutea, number of implantations, implantation rate and number of live fetuses were not affected by TCZ. In fetuses, no effects of TCZ were noted on sex ratio, frequency of visceral or skeletal anomalies, frequency of skeletal variations and number of ossified sacral and caudal vertebrae. In addition, no external anomalies were noted. The toxicological no-effect dose for maternal toxicity, embryo/fetal toxicity and developmental toxicity is 50 mg/kg bw
Embryo-fetal development IV	Once-daily from Day 20 to 50 of gestation	Monkey (cynomolgus) (4–9 years-old)	10 F	0, 2, 10, 50	No maternal deaths occurred in any group. Abortion or embryo-fetal death was noted in one female in each of the control and 2 mg/kg groups (10%), in 2 females in the 10 mg/kg group (20%) and in 3 females in the 50 mg/kg group (30%). No treatment-related abnormalities were noted in maternal clinical signs, body-weight, food consumption or hematological examinations. In those pregnancies carried to term, observations at Caesarean section showed no fetal deaths and no treatment-related effects on fetal weight, placental weight, external measurements, organ weight, external fetal appearance, placental, visceral or skeletal findings. The toxicological no-effect dose for general maternal toxicity is 50 mg/kg and the toxicological no-effect dose for reproductive function in dams and embryo-fetal development is 2 mg/kg.
Male fertility	Once every 3 days, for 63 days before mating, and through the mating period until the day before gross pathology	Mouse	30	15 and 50 mg/kg	MR16-1 had no adverse effects on functional effects of males (on libido, insemination, epididymal sperm maturation and successful fertilization), at either dose of 15 or 50 mg/kg administered intravenously once every three days. Repeated dosing of MR16-1 was associated with death of a few animals due to immunological reactions towards MR16-1, a rat IgG1 antibody. The toxicological no-effect dose level for male fertility is 50 mg/kg bw.
Female fertility	Once every 3 days, for 14 days before mating, and through the mating period, and to Day 6 of gestation	Mouse	30	15 and 50 mg/kg	MR16-1 had no adverse effects on estrous cycle, fertilization, tubal transport, implantation or embryonic development during the preimplantation stage at either dose of 15- or 50-mg/kg administered intravenously once every three days. Repeated dosing of MR16-1 was associated with death of a few animals due to immunological reactions towards MR16-1, a rat IgG1 antibody. The toxicological no-effect dose level for female fertility and early embryonic development is 50 mg/kg bw.

Table 20: Summary of Toxicology Studies (Cont.)

Study Type	Treatment Duration	Species/ Test system	Animals/ group	Dose (mg/kg/day)	Results
Reproductive toxicology (cont.)					
Pre- and postnanal development	Once every 3 days, from day 6 of gestation through to weaning (day 21 after delivery)	Mouse	30	15 and 50 mg/kg	MR16-1 had no adverse effects on the pup viability after birth, development, behavior, learning, immune status (blood, spleen and thymus) and immune function parameters (IgM and IgG responses towards KLH immunization) or reproductive ability of the F1-generation, at either dose of 15 or 50 mg/kg administered intravenously to F0-females. Maternal deaths (~22%) and effects on live birth- and viability indices observed exclusively at the low dose are considered to be associated with an immunoreaction of mother animals towards the foreign MR16-1 protein, and are considered not to impact the study objective. The toxicological no-effect dose level for pregnant and lactating females, and the development of the F_1 generation is 50 mg/kg bw.
Other studies					
Local tolerance IV; SC (perivenous)	Single dose	Rabbit (New Zealand White) (13 week-old)	12 M	IV: 0.5mL/site SC: 0.2mL/site	Irritant property of TCZ formulation was equal to saline.
Local tolerance SC	Single dose	Rabbit (Russian Himalayan) (4 month-old)	3M, 3F	80 mg/0.8 mL/site	Neither macroscopic nor microscopic findings that could be considered related to the test item were observed at the injection site.
Local tolerance IV	Single dose	Rabbit (New Zealand White)	6 M	100 mg/0.5 mL	TCZ was well-tolerated when injected intravenously into rabbits, and did not induce treatment-related irritation at the injection site.
Local tolerance IM	Single dose	Rabbit (Japanese White)	6 M	100 mg/1 mL	The local tolerance reactions of TCZ were similar to those in the physiological saline group.
Local tolerance SC	Single dose	Rabbit (New Zealand White)	6 M	100 mg/0.2 mL	MRA was well-tolerated when injected intravenously into rabbits, and did not induce treatment-related irritation at the injection site.

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PART III: CONSUMER INFORMATION

PrACTEMRA®

tocilizumab

Pronounced: ac-TEM-ra

This leaflet is part III of a three-part "Product Monograph" published when ACTEMRA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACTEMRA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

ACTEMRA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA) and familiar with the ACTEMRA efficacy and safety profile.

What the medication is used for:

ACTEMRA (also known as tocilizumab), is a medicine that is used to treat adults with moderate to severe rheumatoid arthritis. ACTEMRA is also used to treat active systemic juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic arthritis (pJIA) in patients aged 2 and above.

It is not known if ACTEMRA is safe and effective in children with sJIA or pJIA under 2 years of age or in children with conditions other than sJIA or pJIA.

What ACTEMRA does:

ACTEMRA is a medicine that helps keep the immune system from attacking healthy tissues in the body. A normal immune system leaves healthy body tissues alone. In people with rheumatoid arthritis, the immune system attacks normal body tissues causing damage and inflammation, especially in the tissues of your joints. ACTEMRA interferes with an important step in this attack (blocks a cytokine called IL-6 which is found at high levels in the joints affected by rheumatoid arthritis). By decreasing the immune system's attack on normal tissues, ACTEMRA can reduce pain, joint inflammation and tiredness leading to a better quality of life*

What is IL-6?: interleukin-6 is a protein that is made by the immune system and the body uses IL-6 to manage infections. It also plays a major role in the signs and symptoms of rheumatoid arthritis (RA). People with RA have too much IL-6.

When it should not be used:

If you are allergic to tocilizumab or any other non-medicinal ingredient in ACTEMRA, you should not take ACTEMRA.

You should not take ACTEMRA if you have an active infection.

What the medicinal ingredient is:

The active ingredient of ACTEMRA is called tocilizumab.

What the nonmedicinal ingredients are:

Disodium phosphate dodecahydrate, polysorbate 80, sodium dihydrogen phosphate dihydrate, sucrose, water for injections.

What dosage forms it comes in:

ACTEMRA is supplied as a solution for intravenous infusion and is available in vials containing of 80, 200 or 400 mg of tocilizumab.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious Infections: Serious infections have been reported in patients receiving ACTEMRA and other biologic therapies, including tuberculosis (TB) and infections caused by viruses, bacteria or fungi. Some infections have resulted in death. Seek medical attention immediately if you develop symptoms such as fever, persistent cough, weight loss, throat pain or soreness, wheezing, red or swollen skin blisters, tears, wounds, severe weakness or tiredness.

Gastrointestinal perforations: GI perforations (holes in the lining of the gut) have been reported uncommonly, usually as a complication of diverticulitis (infection of the large intestine) and requires immediate medical attention. If you develop fever and severe stomach pain that does not go away, seek medical attention.

Abnormalities of your lab results: your physician will be monitoring your blood work and may notice that your levels are either too high or too low; 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.

Malignancies: During the clinical trials, cases of cancer have been reported very rarely in patients receiving ACTEMRA. The current number of reported cases in the ACTEMRA studies appears to be consistent with the expected number of cancer cases reported in the RA population. The role of treatment with ACTEMRA on the development of cancers is not known.

Nervous system disorders: neurologic symptoms have been observed rarely in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.

Allergic Reactions: Serious allergic reactions, including death can happen with ACTEMRA. These reactions can occur on the first infusion, even if you have taken the premedication and can happen with future infusions of ACTEMRA. Tell your healthcare provider 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.

Treatment with ACTEMRA should not be initiated in patients with active infections.

BEFORE you use ACTEMRA talk to your doctor or pharmacist if:

- You have ever had a bad reaction to tocilizumab or any of the non-medicinal ingredients.
- You are allergic to other medications, food or dyes.
- You are taking any other medications, including but not limited to corticosteroids. You can take other medicines provided your doctor has prescribed them and has told you it is ok to take them while you are taking ACTEMRA. You should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.
- You have any kind of infection, or if you often get infections. Treatment with ACTEMRA could cause your infection to get worse. Tell your doctor immediately if symptoms from an infection occur (see warning box above)
- You have diabetes, HIV/AIDS or a weaker immune system, which can increase your risk of serious infections;
- You live or have lived, or have travelled to certain parts of the world 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.
- You are scheduled to have surgery.
- You have recently had a vaccination or are planning to have a vaccination. You or your child should be brought up to date (if possible) on all recommended vaccinations, *prior to initiation of therapy* with ACTEMRA. Certain vaccines should not be given *while* receiving ACTEMRA.
- You have tuberculosis (TB), or if you have been in close contact with someone who has had TB. Your doctor should test you for TB before starting treatment with ACTEMRA.
- You have hepatitis or any disease of the liver.
- You have had any type of cancer
- You have disease of the nerves or nervous system, such as multiple sclerosis
- You have a history of macrophage activating syndrome (MAS), a rare but serious immune reaction in patients with systemic juvenile idiopathic arthritis.
- You have abdominal pain or have been diagnosed with stomach, pancreas or bowel (intestine) problems, including ulcers, inflammation or infection, including diverticulitis and pancreatitis
- You have high blood pressure
- You are pregnant or plan on becoming pregnant or are breast-feeding a child.

Pregnancy Registry: A pregnancy registry has been established to monitor the outcomes of pregnant women exposed to ACTEMRA. Women who become pregnant while taking ACTEMRA are encouraged to register themselves by calling 1-877-311-8972.

ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

This information will help your doctor and you decide whether you should use ACTEMRA and what extra care may need to be taken while you are on the medication.

Any medicine can have side effects. Like all medicines that affect your immune system, ACTEMRA can cause serious side effects. The possible serious side effects are listed above.

This is not a complete list of side effects. For any unexpected effects while taking ACTEMRA, contact your doctor or pharmacist.

INTERACTIONS WITH THIS MEDICATION

Before starting treatment, make sure your doctor knows if you are taking or have recently taken any other medicines (including those you have bought for yourself from a pharmacy, supermarket or health store). This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect. ACTEMRA should not be used with other drugs unless your doctor has told you it is safe to do so.

ACTEMRA is not to be used with biological medicines that are used to treat rheumatoid arthritis including: Enbrel®, Humira®, Remicade®, Rituxan®, Orencia®, Kineret®, Simponi®, Cimzia®. ACTEMRA has not been studied in combination with these biological medicines.

PROPER USE OF THIS MEDICATION

Your doctor has prescribed ACTEMRA after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours.

Usual dose:

The recommended starting dose of ACTEMRA for adult patients is 4 mg per kg of body weight with an increase to 8 mg per kg of body weight, based on how you respond to the drug.

ACTEMRA will be given to you by a healthcare professional using an intravenous line. This means the medicine will be given to you through a needle placed in a vein in your arm. It will take about 1 hour to give you the full dose of medicine.

ACTEMRA should be given once every 4 weeks. Your doctor will advise you on how long you will continue to be treated with ACTEMRA.

The recommended dose for children with sJIA is either 8 or 12 mg per kg of body weight depending on the child's weight. Children with sJIA receive a dose of ACTEMRA every 2 weeks

The recommended dose for children with pJIA is either 8 or 10 mg per kg of body weight depending on the child's weight. Children with pJIA receive a dose of ACTEMRA every 4 weeks.

Overdose:

Because ACTEMRA is given by a doctor or nurse, it is unlikely that you will be given too much. However, if you are worried then talk to your doctor. If necessary, you will be monitored closely for any signs and symptoms of overdose and be treated for those symptoms as necessary.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have missed your dose of ACTEMRA, ask your doctor when to schedule your next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well while you are receiving treatment with ACTEMRA.

The most common side effects of ACTEMRA are upper respiratory tract infections (common cold, sinus infections) headaches, and increase in blood pressure.

In pJIA the most common side effects of ACTEMRA were upper respiratory tract infections, nausea, headache dizziness, decrease in blood pressure and rash.

Possible serious side effects include serious infections, and allergic reactions.

Stop taking ACTEMRA and call your doctor or seek medical attention immediately if you notice any of the following:

- Difficulty with breathing or light-headedness.
- Rash, itching, hives, swelling of the lips or other signs of an allergic reaction.
- Chest pain.
- Feeling dizzy or faint.

Tell your doctor as soon as possible if you notice any of the following: signs of infection such as fever and chills, mouth or skin blisters, stomach ache or persistent headaches.

The symptoms described above can be signs of the side effects listed in the table below, all of which have been observed with ACTEMRA in controlled clinical trials:

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Side effects		**Talk to your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	Upper respiratory tract infections like coughs and cold, pneumonia, cellulitis (skin infection)		✓	
Common	Cold sores (oral herpes simplex), blisters, shingles (herpes zoster), skin infection sometimes with fever and chills. low white blood cell counts, shown by blood tests, high blood fats (cholesterol levels), headache, dizziness, high blood pressure, mouth ulceration, stomach pain, abnormal liver function tests, rash and itching. In addition in sJIA: ear infection, chicken pox, gastroenteritis (nausea, vomiting, diarrhea), MAS (macrophage activation syndrome)		✓	
Uncommon	Diverticulitis (fever, nausea, diarrhea, constipation, stomach pain,), red swollen (inflamed) areas in the mouth, high blood fat (triglyceride levels) and serious allergic reactions. Pancreatitis: Stomach pain, back pain, nausea, vomiting, Lung disease: shortness of breath, trouble breathing, cough		✓	✓
Rare	Multiple Sclerosis (including blurred vision, loss of vision, eye pain, feeling dizzy, or numbness, weakness or tingling in the face, arms or legs)		✓	✓

Very common: at least 1 in 10 patients; Common: at least 1 in 100 and less than 1 in 10 patients; Uncommon: at least 1 in 1,000 and less than 1 in 100 patients

HOW TO STORE IT

Your ACTEMRA vials should be stored under refrigeration (2-8°C) and protected from light. Your healthcare professional will prepare the solution for intravenous (IV) administration.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- **Fax toll-free to 1-866-678-6789**
- **Mail to: Canada Vigilance Program**
  Health Canada
  Postal Locator 0701D
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.rochecanada.com or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited

Last revised:

* a measurement called HAQ was used to quantify disability (dressing, grooming, eating, walking, hygiene, reach, grip, activities)