Actemra®
Tocilizumab

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug
Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass.
ATC Code: L04AC07.

1.2 Type of Dosage Form
Intravenous (IV) formulation: Concentrate solution for infusion.
Subcutaneous (SC) formulation: Solution for injection (injection).

1.3 Route of Administration
Intravenous (IV) infusion.
Subcutaneous (SC) injection.

1.4 Sterile / Radioactive Statement
Sterile.

1.5 Qualitative and Quantitative Composition
Active ingredient: tocilizumab.

Tocilizumab solution for intravenous (IV) infusion is a clear to opalescent, colourless to pale yellow liquid, supplied in preservative-free, non-pyrogenic single-use vials.
Tocilizumab is supplied in 10 ml and 20 ml vials containing 4 ml, 10 ml or 20 ml of tocilizumab (20 mg/ml).
Excipients: Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections.

Tocilizumab solution for subcutaneous (SC) injection is a yellowish, preservative-free liquid supplied in a ready-to-use, single-use pre-filled syringe with needle safety device (PFS+NSD). Each pre-filled syringe delivers 0.9 mL (162 mg) of tocilizumab.
Excipients: L-histidine, L-histidine hydrochloride monohydrate, L-arginine hydrochloride, L-methionine, polysorbate 80 and water for injection.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)
Rheumatoid Arthritis [IV and SC formulations]
Actemra, in combination with methotrexate (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs), is indicated for:
- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX [IV formulation only]
- the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists [IV and SC formulations]

In these patients, Actemra can be used alone in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV formulation only]
Actemra is indicated in combination with methotrexate (MTX) for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Actemra can be given alone in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Systemic Juvenile Idiopathic Arthritis (sJIA) [IV formulation only]
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 NSAIDS and systemic corticosteroids. Actemra can be given alone or in combination with MTX.

Chimeric Antigen Receptor (CAR) T cell-induced severe or life-threatening Cytokine Release Syndrome (CRS) [IV formulation only]
Actemra is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

2.2 Dosage and Administration
Substitution by any other biological medicinal product requires the consent of the prescribing physician.
The safety and efficacy of alternating or switching between Actemra and products that are biosimilar but not deemed interchangeable to Actemra has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

Intravenous Administration
Actemra IV formulation is not intended for subcutaneous administration.
Actemra IV formulation should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (*see section 4.2 Special Instructions for Use, Handling and Disposal*).
Actemra is recommended for IV infusion over 1 hour.

Subcutaneous Administration
Actemra SC formulation is not intended for intravenous administration.
Actemra SC formulation is administered with a single-use PFS+NSD. The first injection should be performed under the supervision of a qualified health care professional. A patient can self-inject ACTEMRA only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and has been trained in proper injection technique. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.
Patients who transition from Actemra IV therapy to SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified health care professional.
Assess suitability of patient or parent/guardian for SC home administration and instruct the patient or parent/guardian to inform a healthcare professional before administering the next dose, if any symptoms of allergic reaction are experienced. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (*see section 2.4.1 Warnings and Precautions, Genera*l and *2.6 Undesirable Effects*).

Rheumatoid Arthritis (RA) [IV and SC formulations]
Intravenous Dosing Regimen:
The recommended dose of Actemra for adult patients is 8 mg/kg, but no lower than 480 mg, given once every four weeks.
Doses above 1.2 g have not been evaluated in clinical studies.
Actemra should be diluted to 100 ml by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (*see section 4.2 Special Instructions for Use, Handling and Disposal*).
Actemra is recommended for IV infusion over 1 hour.
For individuals whose body weight is more than 100 kilograms (kg), doses exceeding 800 mg per infusion are not recommended (*see Section 3.2 Pharmacokinetic Properties*)

Subcutaneous Dosing Regimen:
The recommended dose of Actemra for adult patients is 162 mg given once every week as a subcutaneous injection. Actemra can be used alone or in combination with MTX and/or other DMARDs.

Dose Modification Recommendations for RA
(See Section 2.4.1 Warnings and Precautions, General)
- Liver enzyme abnormalities

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For patients on intravenous Actemra with persistent increases in this range, reduce Actemra dose to 4 mg/kg or interrupt Actemra until ALT/AST have normalized. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate. For patients on subcutaneous Actemra with persistent increases in this range, reduce Actemra injection frequency to every other week or interrupt Actemra until ALT/AST have normalized. Restart with weekly injection or injection every other week, as clinically appropriate.
> 3 to 5x ULN (confirmed by repeat testing, see section 2.4.4).	Interrupt Actemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue Actemra
> 5x ULN	Discontinue Actemra

- Low absolute neutrophil count (ANC)

Lab Value (cells x 10^9/l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Actemra dosing For patients on intravenous Actemra, when ANC > 1 x 10^9/L resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. For patients on subcutaneous Actemra, when ANC > 1 x 10^9/L resume Actemra injection every other week and increase frequency to every week, as clinically appropriate.
ANC < 0.5	Discontinue Actemra

- Low platelet count

Lab Value (cells x 10^3/µl)	Action
50 to 100	Interrupt Actemra dosing For patients on intravenous Actemra, when platelet count is > 100 x 10^3/µL resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. For patients on subcutaneous Actemra, when platelet count is > 100 x 10^3/µL resume Actemra injection every other week and increase frequency to every week, as clinically appropriate.
< 50	Discontinue Actemra

Cytokine Release Syndrome (CRS) (adults and paediatrics) [IV formulation only]
The recommended dose of Actemra for treatment of patients with CRS given as a 60-minute intravenous infusion is:
- 12 mg/kg for patients below 30 kg,
- 8 mg/kg for patients ≥ 30 kg,

Actemra can be used alone or in combination with corticosteroids.
If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of Actemra may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients.

Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the underlying malignancy, preceding lymphodepleting chemotherapy or the CRS.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV formulation only]
The recommended dose of Actemra for patients with pJIA is:
- 10 mg/kg for patients below 30 kg,
- 8 mg/kg for patients ≥ 30 kg,

given 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 can be used alone or in combination with MTX.

Systemic juvenile idiopathic arthritis (sJIA) [IV formulation only]
The recommended dose of Actemra for patients with sJIA is:
- 12 mg/kg for patients below 30 kg,
- 8 mg/kg for patients ≥ 30 kg,

given once every two 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 can be used alone or in combination with MTX.
Actemra should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (*see section 4.2 Special Instructions for Use, Handling and Disposal*).
Actemra is recommended for IV infusion over 1 hour.

Dose Modification Recommendations 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 Section 2.4.1 Warnings and Precautions, General*). If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and Actemra dosing interrupted until the clinical situation has been evaluated. In pJIA or sJIA the decision to discontinue Actemra for a laboratory abnormality should be based upon the medical assessment of the individual patient.

2.2.1 Special Dosage Instructions
Pediatric use: The safety and efficacy of Actemra intravenous formulation in paediatric patients below the age of 2 years old have not been established. The safety and efficacy of Actemra subcutaneous formulation in children from birth to less than 18 years have not been established. No data are available

Geriatric use: No dose adjustment is required in elderly patients> 65 years of age.

Renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment (*see section 3.2.3 Pharmacokinetics in Special Populations*). Actemra has not been studied in patients with severe renal impairment.

Hepatic impairment: The safety and efficacy of Actemra has not been studied in patients with hepatic impairment (*see section 2.4.1 Warnings and Precautions, General*).

2.3 Contraindications
Actemra is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients.
Active, severe infections.

2.4 Warnings and Precautions
2.4.1 General
In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

All Indications
Infections
Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra (*see section 2.6, Undesirable Effects*). Actemra treatment should not be initiated in patients with active infections. Administration of Actemra should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of Actemra in patients with a history of recurring infection or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections.
Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents, such as Actemra, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. Patients (which include younger children who may be less able to communicate their symptoms) and parents/guardians of minors should be instructed to contact a healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Complications of diverticulitis
Events of diverticular perforation as complications of diverticulitis have been reported in patients treated with Actemra. Actemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated promptly for early identification of gastrointestinal perforation.

Tuberculosis
As recommended for other biologic therapies in all patients should be screened for latent tuberculosis infection prior to starting Actemra therapy. Patients with latent tuberculosis should be treated with standard anti-mycobacterial therapy before initiating Actemra.

Vaccinations
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.
In a randomized open-label study, adult RA patients treated with Actemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. The data demonstrated a small attenuation in the immune response to the 23-valent pneumococcal polysaccharide with ACT + MTX compared with MTX alone, but the response to tetanus toxoid vaccine in each treatment group was similar.
It is recommended that all patients, particularly pediatric or elderly patients, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Actemra therapy. The interval between live vaccinations and initiation of Actemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Actemra (*see section 2.6.1 Undesirable Effects, Clinical Trials*). In the post marketing setting, events of serious hypersensitivity and anaphylaxis have occurred in patients treated with a range of doses of Actemra, with or without concomitant therapies, premedication, and / or a previous hypersensitivity reaction. In the post marketing setting, cases with a fatal outcome have been reported with intravenous Actemra. These events have occurred as early as the first infusion of Actemra (*see sections 2.3 Contraindications and 2.6.2 Post Marketing*). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with Actemra. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately and Actemra should be permanently discontinued (*see section 2.2 Dosage and Administration*).

Active Hepatic Disease and Hepatic Impairment
Treatment with Actemra particularly when administered concomitantly with methotrexate, may be associated with elevations in hepatic transaminases (*see section 2.6.1.Undesirable Effects, Clinical Trials*). Therefore caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment, as the safety of Actemra in these patients has not been adequately studied (*see section 2.2.1 Special Dosage Instructions*).

Hepatotoxicity
Mild and moderate elevations of hepatic transaminases have been observed with Actemra treatment (*see section 2.6.1.Undesirable Effects, Clinical Trials*). Increased frequency of these elevations was observed when drugs), which are known to cause hepatotoxicity (e.g. methotrexate (MTX) were used in combination with Actemra.
Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with Actemra (see section 2.6.2 Undesirable Effects, Post Marketing Experience). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of Actemra. Cases of liver failure resulting in liver transplantation have been reported.
Caution should be exercised when considering initiation of Actemra treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x ULN treatment is not recommended.
Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the underlying malignancy, preceding lymphodepleting chemotherapy or the CRS. The decision to administer Actemra should take into account the potential benefit of treating the CRS versus the risks of short-term treatment with Actemra.
In RA, pJIA and SJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended dose modifications, including Actemra discontinuation, based on transaminases levels, see section 2.2 Dosage and Administration.

Viral reactivation
Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis. In clinical studies with Actemra, patients who screened positive for hepatitis were excluded.

Demyelinating disorders
Physicians should be vigilant for symptoms potentially indicative of new onset central demyelinating disorders. The potential for central demyelination with Actemra is currently unknown.

Neutropenia
Treatment with Actemra was associated with a higher incidence of neutropenia. Treatment-related neutropenia was not associated with serious infection in clinical trials (*see section 2.6.1.Undesirable Effects, Clinical Trials*).
Caution should be exercised when considering initiation of Actemra treatment in patients with a low neutrophil count i.e. absolute neutrophil count (ANC) below 2 x 10^9/L. In patients with an absolute neutrophil count below 0.5 x 10^9/L treatment is not recommended.
In RA, the neutrophil count should be monitored 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on ANC results, see section 2.2 Dosage and Administration.
In pJIA and sJIA, the neutrophil count should be monitored at the time of the second infusion and thereafter according to good clinical practice (*see section 2.2 Dosage and Administration, Dose modifications*).

Thrombocytopenia
Treatment with Actemra was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials (*see section 2.6.1.Undesirable Effects, Clinical Trials*).
Caution should be exercised when considering initiation of Actemra treatment in patients with a platelet count below 100 x 10^3/µL. In patients with a platelet count below 50 x 10^3/µL treatment is not recommended.
In RA, platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on platelet counts, see section 2.2 Dosage and Administration.
In pJIA and sJIA: Platelets should be monitored at the time of the second infusion and thereafter according to good clinical practice (*see section 2.2 Dosage and Administration, Dose modifications*).

Lipids parameters
Elevations of lipid parameters such as total cholesterol, triglycerides and/or low density lipoprotein (LDL) cholesterol have been observed (*see section 2.6.1Undesirable Effects, Clinical Trials*).
In patients treated with Actemra, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

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.

Combination with TNF antagonists
There is no experience with the use of Actemra with TNF antagonists or other biological treatments for RA. Actemra is not recommended for use with other biological agents.

Neurological disorders
Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with Actemra is currently unknown.

Malignancy
The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Infusion reactions
Infusion reactions have been observed during and within 24 hours of treatment with Actemra.

Sodium
This medicinal product contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg. To be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of this medicinal product contain less than 1 mmol sodium (23 mg), i.e. essentially 'sodium free'.

Systemic juvenile idiopathic arthritis [IV formulation only]
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.

2.4.2 Drug Abuse and Dependence
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.

2.4.3 Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machine have been performed. However, there is no evidence from the available data that Actemra treatment affects the ability to drive and use machines.

2.5 Use in Special Populations
2.5.1 Pregnancy
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 higher number of spontaneous abortion /embryo-fetal death at a high dose (*see section 3.3.5 Other*). The relevance of these data for humans is unknown. Women of childbearing potential must use effective contraception during and up to 6 months after treatment. Actemra should not be used during pregnancy unless clearly indicated by medical need.

2.5.2 Nursing Mothers
It is unknown whether Actemra is excreted in human breast milk. Although endogenous immunoglobulins of the IgG isotope are secreted into human milk, a systemic absorption of Actemra via breast feeding is unlikely due to the rapid proteolytic degradation of such proteins in the digestive system. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Actemra should be made taking into account the benefit of breast-feeding to the child and the benefit of Actemra therapy to the woman.

2.5.3 Pediatric Use
See section 2.2.1 Special Dosage Instructions.

2.5.4 Geriatric Use
See section 2.2.1 Special Dosage Instructions, section 3.2.4 Pharmacokinetics in Special Populations.

2.5.5 Renal Impairment
See section 2.2.1 Special Dosage Instructions, section 3.2.4 Pharmacokinetics in Special Populations.

2.5.6 Hepatic Impairment
See section 2.2.1 Special Dosage Instructions, section 3.2.4 Pharmacokinetics in Special Populations.

2.6 Undesirable Effects
2.6.1 Clinical Trials
The safety profile in this section comes from 4510 patients exposed to Actemra in clinical trials; the majority of these patients were participating in RA studies (n=4009), while the remaining experience comes from pJIA (n=240), sJIA (n=112), and GCA (n=149) studies. The safety profile of Actemra across these indications remains similar and undifferentiated.
Adverse Drug Reactions (ADRs) from clinical trials (Table 1) are listed by MedDRA system organ class according to clinical importance to the patient. The corresponding frequency category for each ADR is based on the following convention: very common (≥1/10), common (≥1/100 to < 1/10) or uncommon (≥1/1000 to < 1/100).

Table 1 Summary of ADRs occurring in patients treated with Actemra

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Nervous system disorders		Headache, Dizziness	
Investigations		Hepatic transaminases increased, Weight increased	Total bilirubin increased
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leucopenia, Neutropenia	
Metabolism and nutrition disorders		Hypercholesterolaemia	Hypertriglyceridemia
General disorders and administration site conditions	Injection site reaction	Peripheral oedema, Hypersensitivity reaction	
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Eye disorders		Conjunctivitis	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

Description of selected adverse drug reactions from clinical trials:
Rheumatoid Arthritis
Patients Treated with Intravenous Actemra:
The safety of Actemra has been studied in 5 Phase III, double-blind controlled trials and their extension periods.
The double-blind controlled population includes all patients from the double-blind phases of each core study from randomization until either the first change in the treatment regimen, or two years is reached. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind controlled studies 774 patients received Actemra 4 mg/kg in combination with MTX, 1870 patients received Actemra 8 mg/kg in combination with MTX/other DMARDs and 288 patients received Actemra 8 mg/kg monotherapy.
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, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years.

Infections
In the 6-month controlled trials, the rate of all infections reported with Actemra 8 mg/kg+DMARD treatment was 127 events per 100 patient (pt) years compared to 112 events per 100 pt years in the placebo+DMARD group. In the long-term exposure population the overall rate of infections with Actemra was 108 events per 100 pt years exposure.
In 6-month controlled clinical trials rate of serious infections (bacterial, viral and fungal) with Actemra 8 mg/kg+DMARD was 5.3 events per 100 pt years exposure compared to 3.9 events per 100 pt years exposure in the placebo+DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 pt years of exposure in the Actemra group and 1.5 events per 100 pt years of exposure in the MTX group.
In the long-term exposure population the overall rate of serious infections was 4.7 events per 100 pt years. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, bacterial arthritis. Cases of opportunistic infections have also been reported.

Interstitial Lung Disease
Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Gastrointestinal Perforation
During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 pt years with Actemra therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 pt years. Reports of gastrointestinal perforation on Actemra were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess.

Infusion Reactions
In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the Actemra 8 mg/kg+DMARD and 5.1% of patients in the placebo+DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.
The rate of anaphylaxis (occurring in a total of 6/3778 patients) was several-fold higher in the 4 mg/kg arm in comparison to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with Actemra during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of Actemra (*see section 2.4.1 General Warnings and Precautions*).

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

Early Rheumatoid Arthritis
Study VI (WA19926) evaluated 1162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the Actemra treatment groups was consistent with the known safety profile of Actemra (see Table 1).

Monotherapy: Actemra versus adalimumab
In a 24 week double-blinded, parallel study (monotherapy with Actemra 8 mg/kg IV q4w (N=162) compared to adalimumab 40 mg SC q2w (N=162)), the overall clinical adverse event profile was similar between Actemra and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (Actemra 11.7% vs. adalimumab 9.9%) with the most common event being infections (3.1% each). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with Actemra compared with adalimumab. Four (2.5%) patients in the Actemra arm and two (1.2%) patients in the adalimumab 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 adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/l (25 mg/dL) for patients in the Actemra arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the Actemra arm was consistent with the known safety profile of Actemra and no new or unexpected adverse drug reactions were observed (see Table 1) (*see section 3.1.2 Clinical/Efficacy Studies*).

Patients Treated with Subcutaneous Actemra:
The safety of subcutaneous Actemra in RA was studied in SC-I. The study compared the efficacy and safety of Actemra 162 mg administered every week SC versus 8 mg/kg IV in 1262 subjects with adult RA. All patients in the study received background non-biologic DMARD(s). The safety and immunogenicity observed for Actemra administered SC was consistent with the known safety profile of IV Actemra and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions (ISRs) was observed in the SC arms compared with placebo SC injections in the IV arms (*see section 3.1.2 Clinical/Efficacy Studies*).

Injection Site Reactions (ISRs)
During the 6-month controlled period, in SC-I, the frequency of ISRs was 10.1% (64/631) and 2.4% (15/631) for the SC Actemra and the SC placebo (IV group) weekly injections, respectively. These ISRs (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority was resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity
In SC-I, a total of 625 patients treated with Actemra 162 mg weekly were tested for anti-tocilizumab antibodies in the 6 month controlled period. Five patients (0.8%) developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies.
A total of 1454 SC Actemra all exposure patients have been tested for anti-tocilizumab antibodies, thirteen patients (0.9%) developed positive anti-tocilizumab antibodies, and of these 12 patients (0.8%) developed neutralizing anti-tocilizumab antibodies.
No correlation of antibody development to clinical response or adverse events was observed.

Polyarticular Juvenile Idiopathic Arthritis
Patients Treated with Intravenous Actemra:
The safety of Actemra was studied in 188 pediatric patients, 2 to 17 years of age, with pJIA. The total patient exposure in the Actemra all exposure population was 184.4 patient years. In general, the types of adverse drug reactions in patients with pJIA were similar to those seen in RA and sJIA patients (*see Undesirable Effects section*).

Infections
The rate of infections in the Actemra all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing below30 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 below 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. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients (*see Undesirable Effects section*).
No clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation were reported.

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

Systemic Juvenile Idiopathic Arthritis
Patients Treated with Intravenous Actemra:
The safety of Actemra in sJIA has been studied in 112 pediatric patients 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 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.
In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (*see Undesirable Effects section above*).

Infections
In the 12 week controlled trial the rate of all infections in the Actemra group was 344.7 per 100 patient-years 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 remained similar at 306.6 per 100 patient- years.
In the 12 week controlled trial the rate of serious infections in the Actemra group was 11.5 per 100 patient years. In the on-going open label extension study the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

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, four percent (4.0%) of patients from the Actemra group experienced events occurring during infusion, one event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.
In the 12 week controlled trial experience, 16% of patients in the Actemra group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the Actemra group, the events included, but not limited to rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. 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 (below 1%) treated with Actemra during the controlled and open-label parts of the clinical trial.

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 hypersensitivity reaction leading to withdrawal.

Laboratory Abnormalities
Haematology abnormalities:
Neutrophils
There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections in any of the indications.

Rheumatoid Arthritis
Intravenous Administration:
In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on Actemra 8 mg/kg+DMARD compared to below 0.1% of patients on placebo+DMARD. Approximately half of the instances of ANC below 1 x 10^9/l occurred within 8 weeks of starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving Actemra 8 mg/kg +DMARD (*see sections 2.2 Dosage and Administration, 2.4.1 Warnings and Precautions*).
During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

Subcutaneous Administration:
During routine laboratory monitoring in the Actemra 6-month controlled period of clinical trial SC-I, a decrease in neutrophil count below 1 × 10^9/L occurred in 2.9% of patients on Actemra 162 mg SC weekly.

Polyarticular Juvenile Idiopathic Arthritis
Intravenous Administration:
During routine laboratory monitoring in the Actemra all exposure population, a decrease in neutrophil count below 1 × 10^9/L occurred in 3.7% of patients.

Systemic juvenile idiopathic arthritis
Intravenous Administration:
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, and in none in the placebo group.
In the ongoing open-label extension study decreases in neutrophil counts below 1 x 10^9/L, occurred in 15% of the Actemra group.

Platelets
Rheumatoid Arthritis
Intravenous Administration:
In the 6-month controlled trials decreases in platelet counts below 100 x 10^3 / μL occurred in 1.7% of patients on Actemra 8 mg/kg plus traditional DMARDs compared to below 1% of patients on placebo plus traditional DMARDs, without associated bleeding events (*see sections 2.2 Dosage and Administration, 2.4.1 Warnings and Precautions*).
During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

Subcutaneous Administration:
During routine laboratory monitoring in the Actemra 6-month controlled period of clinical trial SC-I, none of the patients had a decrease in platelet count to ⩽50 × 10^3 / μL.

Polyarticular Juvenile Idiopathic Arthritis
Intravenous Administration:
During routine laboratory monitoring in the Actemra all exposure population, 1% of patients had a decrease in platelet count to ⩽ 50 × 10^3 /μL without associated bleeding events.

Systemic juvenile idiopathic arthritis
Intravenous Administration:
During routine laboratory monitoring in the 12 week controlled trial, 3% of patients in the placebo group and 1% in the Actemra group had a decrease in platelet count to ≤ 100 × 10^3/μL.

In the ongoing open-label extension study decreases in platelet counts below 100 x 10^3 / µL occurred in 3% of patients of the Actemra group, without associated bleeding events.

Liver enzyme elevations

Rheumatoid Arthritis

Intravenous Administration:

During the 6-month controlled trials transient elevations in ALT/AST above 3xULN were observed in 2.1% of patients on Actemra 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received Actemra 8 mg/kg + DMARD compared to 1.5% of patients on placebo+DMARD. The addition of potentially hepatotoxic drugs (e.g. MTX) to Actemra monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST above 5xULN were observed in 0.7% of Actemra monotherapy patients and 1.4% of Actemra+DMARD patients, the majority of whom were discontinued from Actemra treatment (*see sections 2.2 Dosage and Administration, 2.4.1 Warnings and Precautions*). During routine laboratory monitoring, the incidence of indirect bilirubin greater than the upper limit of normal was 6.2% in patients treated with 8 mg/kg Actemra + DMARD in the *double-blind controlled* population.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

In Study WA25204, of the 1538 patients with moderate to severe RA (*see Section 3.1.2 Clinical/Efficacy Studies*) and treated with Actemra, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug induced hepatitis with hyperbilirubinemia was reported in association with Actemra treatment (*see section 2.4.1 Warnings and Precautions*).

Subcutaneous Administration:

During routine laboratory monitoring in the Actemra 6-month controlled period of clinical trial SC-I, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively on SC weekly.

Polyarticular Juvenile Idiopathic Arthritis

Intravenous Administration:

During routine laboratory monitoring in the Actemra all exposure population, elevation in ALT or AST ≥3 x ULN occurred in 3.7% and below 1% of patients, respectively.

Systemic juvenile idiopathic arthritis

Intravenous Administration:

During routine laboratory monitoring in the 12 week controlled trial, elevation in ALT or AST ≥ 3xULN 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 ≥ 3xULN occurred in 12% and 4% of patients, respectively, in the Actemra group.

Elevations in lipid parameters

Rheumatoid Arthritis

Intravenous Administration:

During routine laboratory monitoring in the 6-month controlled trials elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed in patients treated with Actemra. Approximately 24% of patients receiving Actemra in clinical trials experienced sustained elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL).

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

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled clinical trials.

Subcutaneous Administration:

During routine laboratory monitoring in the Actemra 6-month controlled period of clinical trial SC-I, 19% of patients on SC weekly experienced sustained elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 9% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) on SC weekly.

Polyarticular Juvenile Idiopathic Arthritis

Intravenous Administration:

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

Systemic juvenile idiopathic arthritis

Intravenous Administration:

During routine laboratory monitoring in the 12 week controlled trial, elevation in total cholesterol above 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 above 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.

CRS Patients

The safety of Actemra in CRS has been studied in a retrospective analysis of data from clinical trials, where 51 patients were treated with Actemra 8 mg/kg (12 mg/kg for patients less than 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CAR T-cell-induced CRS. A median of 1 dose of Actemra (range, 1-4 doses) was administered.

2.6.2 Post Marketing Experience

The following adverse drug reactions have been identified from post marketing experience with Actemra (Table 1a) based on spontaneous case reports, literature cases and cases from non-interventional study programs. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1a: Adverse drug reactions from post marketing experience

Adverse reaction (MedDRA)	Incidence[4]	Frequency Category
Immune System Disorders		
Anaphylaxis (fatal)[1, 2]	Not observed in clinical trials	Rare
Skin and Subcutaneous Tissue Disorders		
Stevens-Johnson syndrome[3]	Not observed in clinical trials	Rare
Blood and lymphatic system disorders		
Hypofibrinogenemia	1.3 per 100 patient years	Common
Hepatobiliary disorders		
Drug-induced liver injury	0.2 per 100 patient years	Rare
Hepatitis	0.035 per 100 patient years	Rare
Hepatic failure	0.004 per 100 patient years	Very Rare
Jaundice[3]	Not observed in clinical trials	Rare

[1] See section *2.3 Contraindications*

[2] See section *2.4.1 Warnings and Precautions, General*

[3] This adverse reaction was identified through post marketing surveillance but not observed in clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to ACT in clinical trials.

[4] Incidence rate calculated based on all-exposure data obtained from relevant completed clinical trials for all indications.

2.7 Overdose

There are limited data available on overdosage with Actemra. 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.

2.8 Interactions with other Medicinal Products and other Forms of Interaction

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs or corticosteroids on Actemra clearance in RA patients.

Concomitant administration of a single dose of 10 mg/kg Actemra with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

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

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as Actemra is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. Actemra normalizes expression of these enzymes.

The effect of Actemra on CYP enzymes (except CYP2C19 and CYP2D6) is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted.

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of Actemra, to the level similar or slightly higher than those observed in healthy subjects.

When starting or stopping therapy with Actemra, patients taking medicinal products, which are individually dose-adjusted and are metabolised via CYP450 3A4, 1A2, or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses of these products may need to be adjusted to maintain their therapeutic effect. Given its long elimination half-life (t1/2), the effect of Actemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

In clinical studies with Actemra in RA, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A and fibrinogen were observed. Increases in hemoglobin levels were observed, through Actemra decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In study WA28119, similar rapid decreases in CRP and ESR were observed along with slight increases in mean corpuscular haemoglobin concentration.

In healthy subjects administered Actemra in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to their lowest 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 Actemra administration (*see section 2.4.1 Warnings and Precautions, General).*

3.1.1 Mechanism of Action

Actemra is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass. Actemra binds 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. IL-6 is a multi-functional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of hematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis, and neoplasia.

The possibility exists for Actemra to affect host defences against infections and malignancies. The role of Il-6 receptor inhibition in the development of malignancies is not known.

3.1.2 Clinical / Efficacy Studies

Rheumatoid Arthritis

The efficacy of intravenously administered Actemra in alleviating the signs and symptoms of rheumatoid arthritis was assessed in five randomized, double-blind, multicenter studies. Studies I-V required patients ≥ age 18 with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria who had at least 8 tender and 6 swollen joints at baseline.

Actemra was administered intravenously every 4 weeks as monotherapy (Study I), in combination with MTX (Studies II, III, V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV).

Study I 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). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study II, a two year study evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of Actemra or placebo were given every four weeks as blinded therapy for 52 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved ACR20 response criteria. At week 52 the co-primary endpoints were prevention of joint damage and improvement in physical function

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of Actemra or placebo were given every four weeks, in combination with stable MTX (10 – 25 mg weekly). Study IV evaluated 1220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg Actemra or placebo were given every four weeks, in combination with the stable DMARD. Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more anti-TNF therapies. The anti-TNF agent was discontinued prior to randomization. Doses of 4 or 8 mg/kg of Actemra or placebo were given every four weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint for studies III-V was the proportion of patients who achieved an ACR20 response at week 24.

The percent of patients achieving ACR 20, 50 and 70 responses in Studies I to V are shown in Table 2.

The efficacy of subcutaneously administered Actemra was assessed in a double-blind, controlled, multicenter study in patients with active RA. The study (SC-I) required patients to be above 18 years of age with active rheumatoid arthritis diagnosed according to ACR criteria and who had at least 4 tender and 4 swollen joints at baseline. All patients received background non-biologic DMARD(s).

Study SC-I evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s). Approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomized 1:1 to receive Actemra SC 162 mg every week or Actemra IV 8 mg/kg every four weeks in combination with nonbiologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results from study SC-I is shown in Table 4.

Table 2 ACR Responses in MTX/Placebo-Controlled Trials (Percent of Patients)

	Study I MTX-Naïve		Study II Inadequate Response to MTX		Study III Inadequate Response to MTX		Study IV Inadequate Response to DMARD		Study V Inadequate Response to TNF Blocking Agent	
Response Rate	**ACT 8 mg/kg N=286**	**MTX N=284**	**ACT 8 mg/kg +MTX N= 398**	**Placebo + MTX N=393**	**ACT 8 mg/kg +MTX N= 205**	**Placebo + MTX N=204**	**ACT 8 mg/kg + DMARD N=803**	**Placebo + DMARD N=413**	**ACT 8 mg/kg +MTX N=170**	**Placebo + MTX N=158**
ACR20										
Week 24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
Week 52			56%***	25%						
ACR50										
Week 24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
Week 52			36 %***	10%						
ACR70										
Week 24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
Week 52			20%***	4%						
MCR† by week 52			7%	1%						

ACT = Actemra

** p<0.05, Actemra vs. placebo+MTX/DMARD*

*** p<0.01, Actemra vs. placebo+MTX/DMARD*

**** p<0.0001, Actemra vs. placebo+MTX/DMARD*

† MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more.

In all studies, 8 mg/kg Actemra-treated patients had statistically significant higher ACR20, 50, 70 response rates at 6 months compared to control. The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 18 months in the on going open label extension studies of Studies I, III-V.

In the 8 mg/kg Actemra-treated patients significant improvements were noted on all individual components of the ACR response (tender and swollen joint counts, patients and physician global assessment, disability index scores (HAQ), pain assessment and CRP compared to patients receiving placebo+MTX/DMARDS in all studies.

Actemra 8 mg/kg treated patients had a statistically significantly greater reduction in disease activity score (DAS28) than patients treated with placebo+DMARD. A good to moderate EULAR response was achieved by significantly more Actemra treated patients compared to patients treated with placebo+DMARD (Table 3).

Table 3 Cross-Study Comparison of DAS and EULAR Responses at Week 24

	Study I MTX Naive		Study II Inadequate Response to MTX		Study III Inadequate Response to MTX		Study IV Inadequate Response to DMARD		Study V Inadequate Response to TNF Blocking Agent	
	ACT 8 mg/kg N=286	**MTX N=284**	**ACT 8 mg/kg +MTX N= 398**	**Placebo + MTX N=393**	**ACT 8 mg/kg +MTX N= 205**	**Placebo + MTX N=204**	**ACT 8 mg/kg + DMARD N=803**	**Placebo + DMARD N=413**	**ACT 8 mg/kg +MTX N=170**	**Placebo +MTX N=158**
Change in DAS28 [mean (Adjusted mean (SE))]										
Week 24	-3.31 (0.12)	-2.05 (0.12)	-3.11 (0.09)***	-1.45 (0.11)	-3.43 (0.12)***	-1.55 (0.15)	-3.17 (0.07)***	-1.16 (0.09)	-3.16 (0.14) ***	-0.95 (0.22)
DAS<2.6 response (%)										
Week 24	33.6%	12.1%	≠ 33.3%***	3.8%	27.5%***	0.8%	30.2%***	3.4%	30.1%***	1.6%
EULAR response (%)										
None	18%	35%	26%	65%	20%	65%	20%	62%	32%	84%
Moderate	42%	48%	34%	29%	41%	32%	40%	33%	31%	15%
Good†	40%	17%	41%***	6%	38%***	3%	40%***	4%	37%***	2%

ACT = Actemra

†The p value compares across all the EULAR categories

** p<0.05, Actemra vs. placebo+MTX/DMARD*

*** p<0.01, Actemra vs. placebo+MTX/DMARD*

**** p<0.0001, Actemra vs. placebo+MTX/DMARD*

≠ In study II, 47% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 33% of patients at week 24.

Table 4 Clinical Response at Week 24 in Subcutaneous Trial (Percent of Patients)

	SC-I[a]	
	ACT SC 162 mg every week + DMARD(s) N=558	ACT IV 8 mg/kg + DMARD(s) N=537
ACR20		
Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50		
Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70		
Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	
Change in DAS28 [adjusted mean]		
Week 24	-3.5	-3.5
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)	
DAS28 < 2.6		
Week 24	38.4%	36.9%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)	
EULAR response (%)		
None	3.3%	4.8%
Moderate	41.7%	42.7%
Good	55.0%	52.4%

ACT = Actemra

a = Per Protocol Population

Major clinical response

After 2 years of treatment with Actemra plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

Radiographic Response – Intravenous Administration
In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving Actemra compared to control (see table below).
In the open-label extension of Study II the inhibition of progression of structural damage in Actemra/MTX-treated patients was maintained in the second year of treatment.

Table 5 Radiographic mean changes at 52 and 104 weeks in Study II

	PBO + MTX (+option of ACT from week 16)	ACT 8 mg/kg + MTX
Changes from baseline to Week 52		
n	294	353
Total Sharp-Genant score	1.17	0.25
Erosion score	0.76	0.15
JSN score	0.41	0.10
Change from week 52 to week 104		
n	294	353
Total Sharp-Genant score	0.79	0.12
Erosion score	0.48	0.07
JSN score	0.31	0.05

PBO - Placebo
MTX - Methotrexate
ACT - Actemra
JSN - Joint space narrowing
All data presented was read together in campaign 2 which consists of the evaluations of the baseline, week 24, week 52, week 80, week 104 and early withdrawal or escape therapy readings taken up to week 104 visit.

Following 1 year of treatment with Actemra/MTX, 83% of patients had no progression of structural damage, as defined by a change in the TSS score of zero or less, compared with 67% of placebo/MTX-treated patients. This remained consistent following 2 years of treatment (83%). Ninety three percent (93%) of patients had no progression between week 52 and week 104.

Radiographic Response – Subcutaneous Administration
The radiographic response of subcutaneously administered Actemra was assessed in a double-blind, controlled, multicentre study in patients with active RA. This study (SC-II) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. Patients were required to be above 18 years of age with active rheumatoid arthritis diagnosed according to ACR criteria and who had at least 8 tender and 6 swollen joints at baseline. In SC-II, 656 patients were randomized 2:1 to Actemra SC 162 mg every other week or placebo, in combination with non-biologic DMARD(s).
In study SC-II, inhibition of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified mean total Sharp score (mTSS). At week 24, inhibition of structural damage was shown, with significantly less radiographic progression in patients receiving Actemra SC compared with placebo (mTSS of 0.62 vs. 1.23, p=0.0149 (van Elteren). These results are consistent with those observed in patients treated with intravenous Actemra.

Quality of Life Outcomes – Intravenous Administration
Clinically significant improvements in disability index (HAQ-DI, Health Assessment Questionnaire Disability Index), fatigue (FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue) and improvement in both the physical (PCS, Physical Component Summary) and mental health (MCS, Mental Component Summary) domains of the SF-36 (Short Form 36) were observed in patients treated with 8 mg/kg Actemra (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs (Table 6).
At week 24, the proportion of 8 mg/kg Actemra treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of above 0.25), was significantly higher than among patients receiving placebo + MTX/DMARDs in all studies.
During the open-label period of Study II the improvement in physical function has been maintained for up to 2 years.

Table 6 Comparison of SF-36, HAQ and FACIT-Fatigue Responses at Week 24

Study I MTX-Naïve		Study II Inadequate Response to MTX		Study III Inadequate Response to MTX		Study IV Inadequate Response to DMARD		Study V Inadequate Response to TNF Blocking Agent	
ACT 8 mg/kg N=286	**MTX N=284**	**ACT 8 mg/kg +MTX N= 398**	**Placebo + MTX N=393**	**ACT 8 mg/kg +MTX N= 205**	**Placebo + MTX N=204**	**ACT 8 mg/kg +DMARD N= 803**	**Placebo +DMARD N=413**	**ACT 8 mg/kg +MTX N=170**	**Placebo + MTX N=158**
Change in PCS [mean (Adjusted mean (SE))]									
10.2 (0.7)	8.4 (0.7)	8.1 (0.6)**	5.6 (0.7)	9.5 (0.8)***	5.0 (1.0)	8.9 (0.4)***	4.1 (0.6)	8.0 (0.9)**	2.2 (1.3)
Change in MCS [mean (Adjusted mean (SE))]									
6.7 (0.9)	5.0 (0.9)	4.2 (0.8)	2.8 (0.9)	7.3 (1.1)**	2.7 (1.3)	5.3 (0.6)**	2.3 (0.7)	4.1 (1.3)	4.1 (1.9)
Change in HAQ-DI [mean (Adjusted mean (SE))]									
-0.70 (0.05)	-0.52 (0.05)	-0.5 (0.04)**	-0.3 (0.04)	-0.55 (0.06)**	-0.34 (0.07)	-0.47 (0.03)***	-0.2 (0.03)	-0.39 (0.05)***	-0.05 (0.07)
Change in FACIT-Fatigue [mean (Adjusted mean (SE))]									
9.3 (0.8)	7.0 (0.8)	6.4 (0.7)	5.4 (0.8)	8.6 (0.9)***	4.0 (1.0)	8.0 (0.5)***	3.6 (0.7)	8.8 (1.0)*	4.2 (1.6)

ACT = Actemra
** p<0.05, Actemra vs. placebo+MTX/DMARD*
*** p<0.01, Actemra vs. placebo+MTX/DMARD*
**** p<0.0001, Actemra vs. placebo+MTX/DMARD*

In study II, changes in PCS, MCS and FACIT-Fatigue at 52 weeks were 10.1***, 5.4 and 8.4**, respectively, in the ACT 8 mg/kg + MTX group compared to 5.6, 3.8 and 5.5, respectively, in the Placebo plus MTX group. At Week 52, the mean change in HAQ-DI was -0.58 in the ACT 8 mg/kg + MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the ACT 8 mg/kg + MTX group (-0.61).

Quality of Life Outcomes – Subcutaneous Administration
In study SC-I, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 for both Actemra SC 162 mg weekly and Actemra IV 8 mg/kg every 4 weeks. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was comparable in the Actemra SC every week group (65.2%) versus the Actemra IV 8 mg/kg group (67.4%), with a weighted difference in proportions of -2.3% (95% CI -8.1, 3.4). The SF-36 summary was split into mental and physical components. The mental component scores were similar between the groups, with a mean change from baseline at week 24 of 6.22 for the SC group and 6.54 for the IV group. The physical component scores were also similar between the groups, with mean change from baseline at week 24 of 9.49 for the SC group and 9.65 for the IV group.

Laboratory Evaluations
Treatment with 8 mg/kg Actemra in combination with DMARD/MTX or as monotherapy resulted in a highly statistically significant improvement in hemoglobin levels compared with placebo + MTX/DMARD (p<0.0001) at week 24. The greatest improvement was observed in patients with chronic anemia associated with RA; mean hemoglobin levels increased by week 2 and remained within normal range through week 24.
A marked decrease in mean levels of acute phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after Actemra administration. Consistent with the effect on acute phase reactants, treatment with Actemra was associated with reduction in platelet count within the normal range.

Monotherapy: Actemra versus adalimumab
Study WA19924 evaluated 326 patients with 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 adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w.
A statistically significant superior treatment effect was seen in favour of Actemra over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 7).

Table 7 Efficacy Results for Study WA 19924

	ADA + Placebo (IV) N = 162	ACT + Placebo (SC) N = 163	p-value[a]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	**-1.8**	**-3.3**	
Difference in adjusted mean (95% CI)	**-1.5 (-1.8, -1.1)**		**<0.0001**
Secondary Endpoints - Percentage of Responders at Week 24 [b]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ⩽ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

[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

MTX naïve, Early RA
Study VI (WA19926), a 2 year study with the planned primary analysis at week 52 evaluated 1162 MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months). Approximately 20% of patients had received prior treatment with DMARDs other than MTX. This study evaluated the efficacy of IV Actemra 4 or 8 mg/kg every 4 weeks/MTX combination therapy, IV Actemra 8 mg/kg monotherapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage for 104 weeks. The primary endpoint was the proportion of patients achieving DAS28 remission (DAS28 below 2.6) at week 24. A significantly higher proportion of patients in the Actemra 8 mg/kg + MTX and Actemra monotherapy groups met the primary endpoint compared with MTX alone. The Actemra 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the Actemra 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints. In this study, ACR/EULAR remission (Boolean and Index) were also analysed as pre-specified exploratory endpoints, with higher responses observed in the Actemra groups. The results from study VI are shown in Table 8.

Table 8 Efficacy Results for Study VI (WA19926) on MTX-naïve, early RA patients

			ACT 8 mg/kg + MTX N=290	ACT 8 mg/kg + placebo N=292	ACT 4 mg/kg + MTX N=288	Placebo + MTX N=287
Primary Endpoint						
DAS28 Remission	Week 24	n (%)	130 (44.8)***	113 (38.7)***	92 (31.9)	43 (15.0)
Key Secondary Endpoints						
DAS 28 remission	Week 52	n (%)	142 (49.0)***	115 (39.4)	98 (34.0)	56 (19.5)
ACR	Week 24	ACR20, n (%)	216 (74.5)*	205 (70.2)	212 (73.6)	187 (65.2)
		ACR50, n (%)	165 (56.9)**	139 (47.6)	138 (47.9)	124 (43.2)
		ACR70, n (%)	112 (38.6)**	88 (30.1)	100 (34.7)	73 (25.4)
	Week 52	ACR20, n (%)	195 (67.2)*	184 (63.0)	181 (62.8)	164 (57.1)
		ACR50, n (%)	162 (55.9)**	144 (49.3)	151 (52.4)	117 (40.8)
		ACR70, n (%)	125 (43.1)**	105 (36.0)	107 (37.2)	83 (28.9)
HAQ-DI (adjusted mean change from baseline)	Week 52		-0.81*	-0.67	-0.75	-0.64
Radiographic Endpoints (mean change from baseline)						
	Week 52	mTSS	0.08***	0.26	0.42	1.14
		Erosion Score	0.05**	0.15	0.25	0.63
		JSN	0.03	0.11	0.17	0.51
		Radiographic Non-Progression n (%) (change from baseline in mTSS of ⩽0)	226 (83)‡	226 (82)‡	211 (79)	194 (73)
Exploratory Endpoints						
Week 24: ACR/EULAR Boolean Remission, n (%)			47 (18.4)‡	38 (14.2)	43 (16.7)‡	25 (10.0)
ACR/EULAR Index Remission, n (%)			73 (28.5)‡	60 (22.6)	58 (22.6)	41 (16.4)
Week 52: ACR/EULAR Boolean Remission, n (%)			59 (25.7)‡	43 (18.7)	48 (21.1)	34 (15.5)
ACR/EULAR Index Remission, n (%)			83 (36.1)‡	69 (30.0)	66 (29.3)	49 (22.4)

mTSS - modified Total Sharp Score
JSN - Joint space narrowing
All efficacy comparisons vs Placebo + MTX. ***p≤0.0001; **p<0.001; *p<0.05;
‡p-value < 0.05 vs. Placebo + MTX, but endpoint was exploratory (not included in the hierarchy of statistical testing and has therefore not been controlled for multiplicity)

Cardiovascular Outcomes
Study WA25204 was a randomized, open-label (sponsor-blinded), 2-arm parallel-group, multi center, non-inferiority, cardiovascular (CV) outcomes trial in patients with a diagnosis of moderate to severe RA. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with ACT compared with a TNF inhibitor standard of care (etanercept [ETA]).
The study included 3,080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying anti-rheumatic drugs, who were aged ⩾50 years with at least one additional CV risk factor beyond RA. Patients were randomized 1:1 to IV ACT 8 mg/kg Q4W or SC ETA 50 mg QW and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events reviewed by an independent and blinded adjudication committee.
Non-inferiority of ACT to ETA for cardiovascular risk was determined by excluding a >80% relative increase in the risk of MACE. The primary endpoint was met such that a >43% increase in the risk of MACE could be excluded (hazard ratio [HR] comparing ACT to ETA = 1.05; 95% CI = 0.77, 1.43).

Polyarticular Juvenile Idiopathic Arthritis
The efficacy of intravenous Actemra was assessed in a three-part study including an open-label extension in children with active polyarticular juvenile idiopathic arthritis (pJIA). 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), followed by Part III, a 64-week open-label period. Eligible patients ≥ 30 kg received Actemra at 8 mg/kg for 4 doses. Patients below 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) of the study. In Part II, patients were randomized to Actemra (same dose received in Part I) or placebo in a 1:1 ratio was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape.
The primary endpoint was the proportion of patients with a JIA ACR30 flare at week 40 relative to week 16. Forty eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of ACT-treated patients. These proportions were statistically significantly different (p=0.0024).
At the conclusion of Part I, JIA ACR 30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.
During the withdrawal phase (Part II), the percent of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in the table below.

Table 9 JIA ACR Response Rates at Week 40 Relative to Baseline (Percent of Patients)

Response Rate	ACT N=82	Placebo N=81
JIA ACR 30	74.4%†	54.3%†
JIA ACR 50	73.2%†	51.9%†
JIA ACR 70	64.6%†	42.0%†

† *p<0.01, Actemra vs. placebo*

Systemic Juvenile Idiopathic Arthritis
The efficacy of intravenous 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 (ACT:placebo = 2:1) to one of two treatment groups, 75 patients received Actemra infusions every two weeks either 8 mg/kg for patients ≥30kg or 12 mg/kg for patients below 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. 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.
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). Eighty five percent (64/75) of the patients treated with ACT and 24.3% (9/37) of placebo patients achieved this endpoint. These proportions were highly significantly different (p<0.0001).The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in the table below. Responses are maintained in the open label extension.

Table 10 JIA ACR Response Rates at Week 12 (Percent of Patients)

Response Rate	ACT N=75	Placebo N=37
ACR 30	90.7%*	24.3%
ACR 50	85.3%*	10.8%
ACR 70	70.7%*	8.1%
ACR 90	37.3%*	5.4%

** p<0.0001, Actemra vs. placebo*

Systemic Features
In those patients treated with Actemra, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording ≥ 37.5°C in the preceding 14 days) at week 12 versus only 21% of placebo patients (p<0.0001) and 64% of Actemra treated patients with rash characteristic of sJIA at baseline were free of rash at week 12 versus 11% of placebo patients (p=0.0008).
There was a highly statistically significant reduction in pain for Actemra treated patients at week 12 in comparison to placebo patients. The adjusted mean change in the pain VAS after 12 weeks of Actemra treatment was a reduction of 41 points on a scale of 0 -100 compared to a reduction of 1 for placebo patients (p<0.0001).
The responses for systemic features are maintained in the on-going open label extension.

Corticosteroid Tapering
Of the 31 placebo and 70 Actemra patients receiving oral corticosteroids at baseline, 8 placebo and 48 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 (p=0.028). Reductions in corticosteroids continued, with 44 patients off oral corticosteroids, at week 44, while maintaining ACR responses.

Quality of Life
At week 12, the proportion of Actemra treated patients showing a minimally clinically important improvement in CHAQ-DI (defined as an individual total score decrease of ≥0.13) was significantly higher than in patients receiving placebo, 77% versus 19% (p<0.0001). Responses are maintained in the on-going open label extension.

Laboratory Parameters
Fifty out of seventy five (67%) patients treated with Actemra had a haemoglobin below LLN at baseline. Forty (80%) of these patients with decreased haemoglobin had an increase in their haemoglobin to within the normal range at week 12, in comparison to only 2 out of 29 (7%) of placebo patients with haemoglobin below LLN at baseline (p<0.0001). Forty four (88%) Actemra patients with decreased haemoglobin at baseline had an increase in their haemoglobin by ≥10 g/L at week 6 versus 1 (3%) placebo patient (p<0.0001).
The proportion of Actemra treated patients with thrombocytosis at baseline who had a normal platelet count at week 12 was significantly higher than in the placebo patients, 90% versus 4%, (p<0.0001).
A marked decrease in mean levels of acute phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after Actemra administration.
A Phase I, multi-centre, open-label, single arm study (NP25737) to evaluate the PK, safety and exploratory PD and efficacy of Actemra over 12 weeks in paediatric sJIA patients (N=11) under 2 years of age was conducted. Patients (treated with stable background therapy of corticosteroids, MTX, or non-steroidal anti-inflammatory drugs) received intravenous Actemra 12 mg/kg every two weeks. Patients who completed the 12-week period could continue to the optional extension period (a total of 52-weeks or until the age of 2 years, whichever was longer).
The primary PK endpoints (C_{max}, C_{min} and AUC_{2weeks}) of ACT at steady-state in this study are within the ranges of these parameters observed in paediatric patients aged 2 to 17 years in Study WA18221.
The types of AEs observed during the 12-week evaluation period of Study NP25737 were consistent with the safety profile observed in the pivotal Phase III study (WA18221). Of the 11 patients aged under 2 years, three experienced serious hypersensitivity reactions, and three developed treatment induced anti-Actemra antibodies after the event. However, due to the small sample size, the low number of events and confounding factors, conclusions could not be drawn.

CRS
The efficacy of Actemra for the treatment of CRS was assessed in a retrospective analysis of data from clinical trials of CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) for hematological malignancies. Evaluable patients had been treated with Actemra 8 mg/kg (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first episode of CRS was included in the analysis. The efficacy population for the tisagenlecleucel cohort included 28 males and 23 females (total 51 patients)

of median age 17 years (range, 3–68 years). The median time from start of CRS to first dose of Actemra was 3 days (range, 0–18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours.
Patients were considered responders if CRS resolved within 14 days of the first dose of Actemra, if no more than 2 doses of Actemra were needed, and no drugs other than Actemra and corticosteroids were used for treatment. Thirty-nine patients (76.5%; 95% CI: 62.5%–87.2%) achieved a response. In an independent cohort of 15 patients (range: 9–75 years old) with axicabtagene ciloleucel-induced CRS, 53% responded.

3.2 Pharmacokinetic Properties

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

Rheumatoid Arthritis

The pharmacokinetics in healthy subjects and RA patients suggest that PK is similar between the two populations.
The table below shows model predicted secondary PK parameters at each of the four approved dose regimens. The population PK (popPK) model was developed from an analysis dataset composed of an IV dataset of 1793 patients from studies WA17822, WA17824, WA18062 and WA18063 and IV and SC dataset of 1759 patients from studies WA22762 and NA25220. C_{mean} is included in the table since for dosing regimens with different inter-dose interval, the mean concentration over the dosing period characterizes the comparative exposure better than AUCτ.

Table 11 Predicted mean ± SD PK parameters at steady-state after IV and SC dosing in RA

	IV		SC	
ACT PK Parameter	**4 mg/kg Q4W**	**8 mg/kg Q4W**	**162 mg Q2W**	**162 mg QW**
C_{max} (mcg/mL)	83.8 ± 23.1	182 ± 50.4	13.2 ± 8.8	49.8 ± 21.0
C_{trough} (mcg/mL)	0.5 ± 1.5	15.9 ± 13.1	5.7 ± 6.8	43.0 ± 19.8
C_{mean} (mcg/mL)	17.8 ± 6.1	56.6 ± 19.3	10.2 ± 8.0	47.4 ± 20.5
Accumulation C_{max}	1.01	1.09	2.12	5.27
Accumulation C_{trough}	2.62	2.47	6.02	6.30
Accumulation C_{mean} or AUC_{τ} *	1.09	1.32	2.67	6.32

*τ = 4 weeks for IV regimens, 2 week or 1 week for the two SC regimens, respectively

At high serum concentrations, when total clearance of Actemra is dominated by linear clearance, a terminal half-life of approximately 21.5 days was derived from the population parameter estimates.
While after IV administration maximum concentration (C_{max}) increased doseproportionally between doses of 4 and 8 mg/kg IV every 4 weeks, a greater than doseproportional increase was observed in the average concentration (C_{mean}) and trough concentration (C_{trough}). At steady-state, C_{mean} and C_{trough} were 3.2 and 32 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively. Exposures after the 162 mg SC QW regimen were greater by 4.6 (C_{mean}) to 7.5 fold (C_{trough}) compared to the 162 SC Q2W regimen.
The accumulation ratios for AUC and C_{max} after multiple doses of 4 and 8 mg/kg Q4W are low, while the accumulation ratios are higher for C_{trough} (2.62 and 2.47). Accumulation ratios after multiple doses of either SC regimen were higher than after IV regimen with the highest ratios for C_{trough} (6.02 and 6.30). The higher accumulation for C_{trough} was expected based on the nonlinear clearance contribution at lower concentrations.
For C_{max}, more than 90% of the steady-state was reached after the 1st IV infusion, and after the 12th SC and the 5th SC injection in QW and Q2W regimens respectively. For AUC_{τ} and C_{mean}, 90% of the steady-state was reached after the 1st and 3rd infusion for the 4 mg/kg and 8 mg/kg IV, respectively, and after the 6th and 12th injections for the 162 mg SC Q2W and QW regimens respectively. For C_{trough}, approximately 90% of the steady-state was reached after the 4th IV infusion, the 6th and 12th injections for the respective SC regimens.
Population PK analysis identified body weight as a significant covariate impacting pharmacokinetics of Actemra. When given IV on a mg/kg basis, individuals with body weight ⩾ 100 kg are predicted to have mean steady-state exposures higher than mean values for the patient population. Therefore, Actemra doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (*see section 2.2 Dosage and Administration)*. Due to the flat dosing employed for SC administration of Actemra, no modifications are necessary by this dosing route.

Polyarticular Juvenile Idiopathic Arthritis

The pharmacokinetics of intravenous Actemra 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 Actemra (patients with a body weight ⩾ 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{trough} of Actemra were 29500 ± 8660 µg·hr/mL, 182 ± 37 µg/mL and 7.49 ± 8.2 µg/mL, respectively.
The following parameters are valid for a dose of 10 mg/kg Actemra (patients with a body weight below 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{trough} of Actemra 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_{trough} for 10 mg/kg (BW below 30 kg) and 8 mg/kg (BW ⩾ 30 kg) doses, respectively. No accumulation for C_{max} was observed.

Systemic Juvenile Idiopathic Arthritis

The pharmacokinetics of intravenous Actemra 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 below 30 kg), given every 2 weeks. The predicted mean (± SD) AUC_{2weeks}, C_{max} and C_{trough} of Actemra were 32200 ± 9960 µg·hr/mL, 245 ±57.2 µg/mL and 57.5 ± 23.3 µg/mL, respectively. The accumulation ratio for C_{trough} (week12/week2) was 3.2 ± 1.3. The Actemra C_{trough} was stabilized after week 12. Mean predicted Actemra exposure parameters were similar between the two body weight groups. The pharmacokinetics of Actemra were similar in paediatric patients under 2 years compared to patients over 2 years of age with a body weight below 30 kg from a regimen of 12 mg/kg IV Actemra given every 2 weeks.

3.2.1 Absorption

Following SC dosing in RA patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 80%.

3.2.2 Distribution

Following IV dosing, Actemra 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.
In pediatric patients with pJIA, the central volume of distribution was 1.98 L, the peripheral volume of distribution was 2.1 L, resulting in a volume of distribution at steady state of 4.08 L.
In pediatric patients with sJIA, the central volume of distribution was 0.94 L, the peripheral volume of distribution was 1.60 L resulting in a volume of distribution at steady state of 2.54 L.

3.2.3 Elimination

The total clearance of Actemra 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 RA patients, 5.8 mL/h in pediatric patients with polyarticular juvenile idiopathic arthritis and 7.1 mL/h in pediatric patients with systemic juvenile idiopathic arthritis. The concentration-dependent nonlinear clearance plays a major role at low Actemra concentrations. Once the nonlinear clearance pathway is saturated, at higher Actemra concentrations, clearance is mainly determined by the linear clearance. Due to dependence of total clearance on Actemra serum concentrations, $t_{1/2}$ of Actemra is also concentration-dependent and can only be calculated at a given serum concentration level. In RA patients, for intravenous administration, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state. At high serum concentrations, when total clearance of Actemra is dominated by linear clearance, a terminal $t_{1/2}$ of approximately 21.5 days was derived from the population parameter estimates.
In children with pJIA, the $t_{1/2}$ of IV Actemra 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 below 30 kg) during a dosing interval at steady state.
In children with sJIA, the $t_{1/2}$ of IV Actemra is up to 23 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight below 30 kg) at Week 12.

3.2.4 Pharmacokinetics in Special Populations

Hepatic Impairment
No formal study of the effect of hepatic impairment on the pharmacokinetics of Actemra was conducted.

Renal Impairment
No formal study of the effect of renal impairment on the pharmacokinetics of Actemra was conducted.
Most of the patients in the RA population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula < 80 ml/min and ≥ 50 ml/min) did not impact the pharmacokinetics of Actemra.
Approximately one-third of the patients in the study WA28119 had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on Actemra exposure was noted in these patients.
No dose adjustment is required in patients with mild or moderate renal impairment.

Other special populations
Population pharmacokinetics analyses in adult RA patients showed that age, sex and race did not affect pharmacokinetics of Actemra. No dose adjustment is necessary for these demographic factors.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

A carcinogenicity study of Actemra has not been conducted. Available preclinical data, showed the contribution of the pleiotropic cytokine IL-6 to malignant progression and apoptosis resistance of various cancer types. These data do not suggest a relevant risk for cancer initiation and progression under therapy with Actemra. Accordingly, proliferate lesions have not been observed in a chronic cynomolgus monkey 6-month toxicity study nor were they described in IL-6 knock-out mice under chronic IL-6 depletion.

3.3.2 Genotoxicity

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

3.3.3 Impairment of Fertility

Nonclinical data do not suggest an effect on fertility under treatment with an analogue of Actemra. Effects on endocrine active organs or on organs of the reproductive system were not seen in a chronic cynomolgus monkey toxicity study, nor was the reproductive performance affected in IL-6 deficient male and female mice.

3.3.4 Reproductive Toxicity

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

3.3.5 Other

In an embryo-fetal toxicity study conducted in cynomolgus monkeys a slight increase of abortion/embryo-fetal death was observed with high systemic cumulative exposure (above 100 times human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. The abortion incidence was within the historical background for the cynomolgus monkey in captivity and the individual cases of abortions/embryo-foetal death did not show any consistent relationship to dosing or duration of dosing with Actemra. Although IL-6 does not seem to be a critical cytokine for either fetal growth or the immunological control of the maternal/fetal interface, a relation of this finding to Actemra cannot be excluded.
Transfer of a murine analogue of Actemra into the milk of lactating mice has been observed.
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.
The non-clinical safety profile of Actemra in the cynomolgus monkey does not suggest a difference between IV and SC routes of administration.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Intravenous Actemra:
This medicine should not be used after the expiry date (EXP) shown on the pack.
For vials: Store between 2ºC – 8ºC, do not freeze. Keep the container in the outer carton in order to protect from light.
For prepared infusion solution: The prepared infusion solution of Actemra is physically and chemically stable in 0.9% w/v sodium chloride solution at 30ºC for 24 hours.
From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2ºC – 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

Subcutaneous Actemra:
This medicine should not be used after the expiry date (EXP) shown on the pack.
Store the pre-filled syringe in a refrigerator at a temperature of 2-8°C. Do not freeze, keep in carton to protect from light, and keep dry.

4.2 Special Instructions for Use, Handling and Disposal

Intravenous Actemra:
Parenteral medications should be inspected visually for particulate matter or discoloration prior to administration.
Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles must be infused.

Use a sterile needle and syringe to prepare Actemra.

Rheumatoid Arthritis and CRS Patients (≥ 30 kg):
From a 100 ml infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the Actemra solution required for the patient's dose. Withdraw the required amount of Actemra (0.4 ml/kg) under aseptic conditions and dilute to a calculated Actemra concentration in a 100 ml infusion bag containing sterile, non-pyrogenic 0.9% Sodium Chloride solution. To mix the solution, gently invert the bag to avoid foaming.

Use in the paediatric population
pJIA, sJIA and CRS Patients ≥ 30 kg:
From a 100 mL infusion bag, withdraw a volume of 0.9% Sodium Chloride solution equal to the volume of the Actemra solution required for the patient's dose. Withdraw the required amount of Actemra (0.4 mL/kg) under aseptic conditions and dilute to a calculated Actemra concentration in a 100 mL infusion bag containing sterile, non-pyrogenic 0.9% Sodium Chloride solution. To mix the solution, gently invert the bag to avoid foaming.

pJIA Patients below 30 kg:
From a 50 mL infusion bag, withdraw a volume of 0.9% Sodium Chloride solution equal to 0.5 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of Actemra under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

sJIA and CRS Patients below 30 kg:
From a 50 mL infusion bag, withdraw a volume of 0.9% Sodium Chloride solution equal to 0.6 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of Actemra under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

Subcutaneous Actemra:
Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to yellowish, or any part of the PFS+NSD appears to be damaged.

Disposal of syringes/sharps
The following points should be strictly adhered to regarding the use and disposal of the PFS+NSD and pre-filled pen:

- Syringes and pre-filled pens should never be reused.
- Place all used syringes and pre-filled pens into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

For home use, patients should procure a puncture resistant container for the disposal of used syringes and pre-filled pens.

Disposal of unused/expired medicines
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.

4.3 Packs

Intravenous Formulation

Vials 80mg/4ml	1, 4
Vials 200mg/10ml	1, 4
Vials 400mg/20ml	1, 4

Subcutaneous Formulation
1 Pre-filled Syringe in a carton
4 Pre-Filled Syringes in a carton

Medicine: keep out of reach of children

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