Actemra®

Tocilizumab

Information as set forth in this label only applies to Actemra

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: Ready-to-use sterile liquid solution in a single-use pre-filled syringe (PFS) with needle safety device (NSD).

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, supplied in 4 mL,10 mL and 20 mL vials containing 80 mg, 200mg, or 400 mg 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 device delivers 0.9 mL (162 mg) of tocilizumab.

Excipients: Polysorbate 80, L-arginine, L-arginine hydrochloride, L-methionine, L-histidine, L-histidine hydrochloride monohydrate and water for injections.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Rheumatoid Arthritis (RA) [IV and SC formulations]

Tocilizumab is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. Tocilizumab can be used alone or in combination with

methotrexate (MTX) and/or other disease-modifying anti-rheumatic drugs (DMARDs). Tocilizumab has been shown to inhibit progression of joint damage as measured by X-ray and to improve physical function.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV formulation only]

Tocilizumab is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. Tocilizumab can be given alone or in combination with MTX.

Systemic Juvenile Idiopathic Arthritis (sJIA) [IV formulation only]

Tocilizumab is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Tocilizumab can be given alone or in combination with MTX.

2.2 Dosage and Administration

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

For adult patients with RA, tocilizumab may be administered as an IV infusion or a SC injection.

For patients with pJIA and sJIA, tocilizumab is administered as an IV infusion.

Tocilizumab 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*).

Tocilizumab is recommended for IV infusion over 1 hour.

Tocilizumab 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. 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.

Rheumatoid Arthritis [IV and SC formulations]

Intravenous Dosing Regimen:

The recommended dose of tocilizumab for adult patients is 8 mg/kg given once every four weeks as an IV infusion. Tocilizumab can be used alone or in combination with MTX and/or other DMARDs.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (*see section 3.2 Pharmacokinetic Properties*).

Tocilizumab IV formulation is not intended for subcutaneous administration.

Subcutaneous Dosing Regimen:

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

Patients transitioning from tocilizumab 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.

Tocilizumab SC formulation is not intended for intravenous administration.

Assess suitability of patient for SC home use and instruct patients to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (*see section 2.4.1 Warnings and Precautions, General*).

Dose Modification Recommendations for RA:

(*see section 2.4.4 Laboratory Tests*)

- Liver enzyme abnormalities

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

- Low absolute neutrophil count (ANC)

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

- Low platelet count

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV formulation only]

The recommended dose of tocilizumab for patients with pJIA is:

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

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. Tocilizumab can be used alone or in combination with MTX.

Systemic Juvenile Idiopathic Arthritis (sJIA) [IV formulation only]

The recommended dose of tocilizumab for patients with sJIA is:

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

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. Tocilizumab can be used alone or in combination with MTX.

Dose Modification Recommendations for pJIA and sJIA:

Dose reduction of tocilizumab has not been studied in the pJIA or sJIA population. Dose interruptions of tocilizumab for laboratory abnormalities are recommended in patients with pJIA or sJIA and are similar to what is outlined above for patients with RA (*also see section 2.4.4 Laboratory Tests*). If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. In pJIA or sJIA the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

2.2.1 Special Dosage Instructions

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

Elderly: No dose adjustment is required in elderly patients aged 65 years and older.

Renal impairment: No dose adjustment is required in patients with mild renal impairment (*see section 3.2.5 Pharmacokinetics in Special Populations*). Tocilizumab has not been studied in patients with moderate to severe renal impairment.

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

2.3 Contraindications

2.3.1 Known hypersensitivity to tocilizumab or to any of the excipients.

2.3.2 Known active, severe infection

2.4 Warnings and Precautions

2.4.1 General

In order to improve the traceability of biological medicinal products, the trade name 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 tocilizumab (*see section 2.6 Undesirable Effects*). Tocilizumab treatment should not be initiated in patients with active infections. Administration of tocilizumab 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 tocilizumab 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 biologic treatments for moderate to severe RA, pJIA or sJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reactants. Patients and parents/guardians of minors with pJIA or sJIA 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 RA patients. Tocilizumab 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 rheumatoid arthritis, pJIA or sJIA, patients should be screened for latent tuberculosis infection prior to starting tocilizumab therapy. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating tocilizumab.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with tocilizumab 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 tocilizumab.

In a randomized open-label study, adult RA patients treated with tocilizumab 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.

It is recommended that all patients, particularly pJIA or sJIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating tocilizumab therapy. The interval between live vaccinations and initiation of tocilizumab 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 tocilizumab (*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 tocilizumab, with or without concomitant arthritis therapies, premedication, and / or a previous hypersensitivity reaction. In the post marketing setting, cases with a fatal outcome have been reported with intravenous tocilizumab. These events have occurred as early as the first infusion

of tocilizumab (*see sections 2.3 Contraindications, 2.6.2 Post Marketing*). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with tocilizumab. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of tocilizumab should be stopped immediately and tocilizumab should be permanently discontinued (*see section 2.2 Dosage and Administration*).

Active Hepatic Disease and Hepatic Impairment

Treatment with tocilizumab particularly when administered concomitantly with methotrexate, may be associated with elevations in hepatic transaminases, therefore caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (*see sections 2.2.1 Special Dosage Instructions, 2.6.1.1 Laboratory Abnormalities*).

Viral reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis. In clinical studies with tocilizumab, 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 tocilizumab is currently unknown.

Systemic Juvenile Idiopathic Arthritis

Macrophage activation syndrome (MAS)

MAS is a serious life-threatening disorder that may develop in patients with sJIA. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS.

Overweight

Monitor side effects in patients with high body weight (> 100 kg)
The response in patients with body weight greater than 100 kg may not be effective as patients who have body weight lower than 100 kg.

2.4.2 Drug Abuse and Dependence

No studies on the effects on the potential for tocilizumab to cause dependence have been performed. However, there is no evidence from the available data that tocilizumab 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 tocilizumab treatment affects the ability to drive and use machines.

2.4.4 Laboratory Tests

Rheumatoid Arthritis, pJIA and sJIA

Neutropenia

Treatment with tocilizumab was associated with a higher incidence of neutropenia. Treatment-related neutropenia was not associated with serious infection in clinical trials (*see section 2.6.1.1 Laboratory Abnormalities*).

Caution should be exercised when considering initiation of tocilizumab treatment in patients with a low neutrophil count i.e. absolute neutrophil count (ANC) $<2 \times 10^9$/l. In patients with an absolute neutrophil count $<0.5 \times 10^9$/l treatment is not recommended.

In RA, neutrophils 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, neutrophils 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 tocilizumab 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 2.6.1.1 Laboratory Abnormalities*).

Caution should be exercised when considering initiation of tocilizumab treatment in patients with a platelet count below $100 \times 10^3/\mu l$. In patients with a platelet count $<50 \times 10^3/\mu l$ 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*).

Hepatic Transaminase Elevations

In clinical trials, mild and moderate elevations of hepatic transaminases have been observed with tocilizumab treatment, without progression to hepatic injury (*see section 2.6.1.1 Laboratory Abnormalities*). Increased frequency of these elevations was observed when potential hepatotoxic drugs (e.g. methotrexate (MTX)) were used in combination with tocilizumab.

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

In RA, ALT and AST should be monitored 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on transaminases, see section 2.2 Dosage and Administration.

In pJIA and sJIA, ALT and AST 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 2.6.1.1 Laboratory Abnormalities*).

In RA, pJIA and sJIA, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of tocilizumab therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

2.4.5 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 tocilizumab clearance.

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

Tocilizumab 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 tocilizumab is introduced.

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

The effect of tocilizumab on CYP enzymes (except CYP2C19 and CYP2D6) is clinically relevant for CYP450 substrates with a narrow therapeutic index, and/or 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 tocilizumab, to the level similar or slightly higher than those observed in healthy subjects.

When starting or stopping therapy with tocilizumab, 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 tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy .

2.4.6 Do not use tocilizumab with other biologic medicines used to treat rheumatoid arthritis, pJIA or sJIA, including infliximab, adalimumab, etanercept, anakinra, abatacept, rituximab, certolizumab pegol and golimumab. It is unknown how tocilizumab interacts with these medicines.

2.5 Use in Special Populations

2.5.1 Pregnancy

There are no adequate data from the use of tocilizumab in pregnant women. A study in monkeys did not indicate any dysmorphogenic potential but has yielded a higher number of spontaneous abortion/embryo-foetal death at a high dose (*see section 3.3.5 Preclinical Safety, Other*). The relevance of these data for humans is unknown.

Tocilizumab should not be used during pregnancy unless clearly indicated by medical need.

2.5.2 Labour and Delivery

No text

2.5.3 Nursing Mothers

It is unknown whether tocilizumab is excreted in human breast milk. Although endogenous immunoglobulins of the IgG isotope are secreted into human milk, a systemic absorption of tocilizumab 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 tocilizumab should be made taking into account the benefit of breast-feeding to the child and the benefit of tocilizumab therapy to the woman.

2.5.4 Paediatric Use

(See section 2.2.1 Special Dosage Instructions.)

2.5.5 Geriatric Use

(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations.)

2.5.6 Renal Impairment

(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations.)

2.5.7 Hepatic Impairment

(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations.)

2.6 Undesirable Effects

2.6.1 Clinical Trials

Rheumatoid Arthritis

Patients Treated with Intravenous Tocilizumab:

The safety of tocilizumab has been studied in 5 Phase III, double-blind controlled trials and their extension periods.

The *all control* 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 tocilizumab 4 mg/kg in combination with MTX, 1870 patients received tocilizumab

8 mg/kg in combination with MTX/other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The *all exposure* population includes all patients who received at least one dose of tocilizumab 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.

ADRs are listed according to clinical importance to the patient. Frequencies are defined as 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 with rheumatoid arthritis receiving tocilizumab treatment as monotherapy or in combination with methotrexate or other DMARDs in the *all control* population

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections	Cellulitis, 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		Peripheral oedema, Hypersensitivity reaction, Injection site reaction	
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Eye disorders		Conjunctivitis	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

Infections

In the 6 month controlled trials, the rate of all infections reported with tocilizumab 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 *all exposure* population the overall rate of infections with tocilizumab was 108 events per 100 pt years exposure.

In 6 month controlled clinical trials rate of serious infections (bacterial, viral and fungal) with tocilizumab 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 tocilizumab group and 1.5 events per 100 pt years of exposure in the MTX group.

In the *all 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 infection

During the 6 month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 pt years with tocilizumab therapy. In the *all exposure* population the overall rate of gastrointestinal perforation was 0.28 events per 100 pt years. Reports of gastrointestinal perforation on tocilizumab 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 tocilizumab 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 tocilizumab and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with tocilizumab during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of tocilizumab (*see section 2.4.1 Warnings and Precautions, General*).

Immunogenicity

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

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 tocilizumab treatment groups was consistent with the known safety profile of tocilizumab (see Table 1) (*see section 3.1.2 Clinical/Efficacy Studies*).

Monotherapy: tocilizumab versus adalimumab

In a 24 week double-blinded, parallel study (monotherapy with tocilizumab 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 tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 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 tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab 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 tocilizumab 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 tocilizumab arm and 0.19 mmol/l (7 mg/dl) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab 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 Tocilizumab:

The safety of subcutaneous tocilizumab in RA was study in SC-I. The study compared the efficacy and safety of tocilizumab 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 tocilizumab administered SC was consistent with the known safety profile of IV tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions 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

During the 6-month controlled period, in SC-I, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the SC tocilizumab and the SC placebo (IV group) weekly injections, respectively. These injection site reactions (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 tocilizumab 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 tocilizumab 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

The safety of intravenous tocilizumab was studied in 188 paediatric patients, 2 to 17 years of age, with pJIA. The total patient exposure in the tocilizumab 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 tocilizumab 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 <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (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 tocilizumab 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 tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity

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

Systemic Juvenile Idiopathic Arthritis

The safety of intravenous tocilizumab in sJIA has been studied in 112 paediatric patients 2 to 17 years of age. In the 12 week double-blind, controlled portion of the clinical trial 75 patients received treatment with tocilizumab (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 tocilizumab 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 tocilizumab 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 tocilizumab 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 tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the tocilizumab group, the events included, but not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events, (urticaria) was considered serious.

Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (<1%) treated with tocilizumab 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.

2.6.1.1 Laboratory Abnormalities

Haematology abnormalities:

Neutrophils

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 tocilizumab 8 mg/kg+DMARD compared to <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 tocilizumab 8 mg/kg +DMARD (*see sections 2.2 Dosage and Administration, 2.4.4 Laboratory Tests*). There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

In the *all control* and *all exposure* population, 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 tocilizumab 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 tocilizumab 162 mg SC weekly.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1×10^9/L occurred in 3.7% of patients.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Systemic Juvenile Idiopathic Arthritis

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 tocilizumab 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 tocilizumab group.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

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 tocilizumab 8 mg/kg plus traditional DMARDs compared to <1% of patients on placebo plus traditional DMARDs, without associated bleeding events (*see sections 2.2 Dosage and Administration, 2.4.4 Laboratory Tests*).

In the *all control* and *all exposure* population, 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 tocilizumab 6-month controlled period of clinical trial SC-I, none of the patients had a decrease in platelet count to $\leq 50 \times 10^3$ / μL.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to $\leq 50 \times 10^3$ / μL without associated bleeding events.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12 week controlled trial, 3% of patients in the placebo group and 1% in the tocilizumab group had a decrease in platelet count to $\leq 100 \times 10^3 / \mu L$.

In the ongoing open-label extension study decreases in platelet counts below $100 \times 10^3 / \mu L$ occurred in 3% of patients of the tocilizumab group, without associated bleeding events.

Liver enzyme elevations

Rheumatoid Arthritis

Intravenous Administration:

During the 6 month controlled trials transient elevations in ALT/AST > 3xULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received tocilizumab 8 mg/kg + DMARD compared to 1.5% of patients on placebo+DMARD. The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST >5xULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab+DMARD patients, the majority of whom were discontinued from tocilizumab treatment (*see sections 2.2 Dosage and Administration, 2.4.4 Laboratory Tests*). These elevations were not associated with any clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency. 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 tocilizumab + DMARD in the *all control* population.

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

In Study VI, MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months) experienced more transient elevations in ALT > 3xULN compared with the *all control* population. This was observed in both tocilizumab treated patients and MTX monotherapy patients.

Subcutaneous Administration:

During routine laboratory monitoring in the tocilizumab 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

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

Systemic Juvenile Idiopathic Arthritis

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 tocilizumab 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 tocilizumab 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 tocilizumab. Approximately 24% of patients receiving tocilizumab in clinical trials experienced sustained elevations in total cholesterol > 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.

In the *all control* and *all exposure* population, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6 month controlled clinical trials.

Subcutaneous Administration:

During routine laboratory monitoring in the tocilizumab 6-month controlled period of clinical trial SC-I, 19% of patients on SC weekly experienced sustained elevations in total cholesterol > 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

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

Systemic Juvenile Idiopathic Arthritis

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

2.6.2 Post Marketing

The safety profile in post marketing experience is consistent with clinical trial data with the exception of reports of fatal anaphylaxis during intravenous tocilizumab treatment (*see sections 2.3 Contraindications, 2.4.1 Warnings and Precautions, General*). Stevens-Johnson Syndrome (SJS) has been reported during treatment with tocilizumab.

2.6.2.1 Laboratory Abnormalities

No text

2.7 Overdose

There are limited data available on overdosage with tocilizumab. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg IV. 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 IV, although dose-limiting neutropenia was observed.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

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

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to 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 tocilizumab administration (*see section 2.4.4 Laboratory Tests).*

3.1.1 Mechanism of Action

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. 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 haematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis, and neoplasia.

The possibility exists for tocilizumab 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 tocilizumab in alleviating the signs and symptoms of rheumatoid arthritis was assessed in five randomized, double-blind, multicentre studies. Studies I-V required patients $\geq$ 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.

Tocilizumab 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 tocilizumab 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 2 year study, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab 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 tocilizumab 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 tocilizumab 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 tocilizumab 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 tocilizumab was assessed in a double-blind, controlled, multicentre study in patients with active RA. The study (SC-I) required patients to be >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 tocilizumab SC 162 mg every week or tocilizumab IV 8 mg/kg every four weeks in combination with non-biologic 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	**TCZ 8 mg/kg N=286**	**MTX N=284**	**TCZ 8 mg/kg +MTX N= 398**	**Placebo + MTX N=393**	**TCZ 8 mg/kg +MTX N= 205**	**Placebo + MTX N=204**	**TCZ 8 mg/kg + DMARD N=803**	**Placebo + DMARD N=413**	**TCZ 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%						

TCZ = tocilizumab

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

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

**** p<0.0001, tocilizumab 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 tocilizumab-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 3 years in the on-going open label extension studies of Studies I -V.

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

Tocilizumab 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 tocilizumab 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	
	TCZ 8 mg/kg N=286	MTX N=284	TCZ 8 mg/kg +MTX N= 398	Placebo + MTX N=393	TCZ 8 mg/kg +MTX N= 205	Placebo + MTX N=204	TCZ 8 mg/kg + DMARD N=803	Placebo + DMARD N=413	TCZ 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%

TCZ = tocilizumab

†The p value compares across all the EULAR categories

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

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

**** p<0.0001, tocilizumab 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]	
	TCZ SC 162 mg every week + DMARD(s) N=558	TCZ 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%

TCZ = tocilizumab

a = Per Protocol Population

Major Clinical Response

After 2 years of treatment with tocilizumab/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 tocilizumab compared to control.

In the open-label extension of Study II the inhibition of progression of structural damage in tocilizumab/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 TCZ from week 16)	**TCZ 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 week104		
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
TCZ Tocilizumab
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 tocilizumab/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 tocilizumab 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 >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 tocilizumab 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 tocilizumab 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 tocilizumab.

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 tocilizumab (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs (Table 6).

At week 24, the proportion of 8 mg/kg tocilizumab treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of >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	
TCZ 8 mg/kg N=286	MTX N=284	TCZ 8 mg/kg +MTX N= 398	Placebo + MTX N=393	TCZ 8 mg/kg +MTX N= 205	Placebo + MTX N=204	TCZ 8 mg/kg + DMARD N= 803	Placebo +DMARD N=413	TCZ 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)

TCZ = tocilizumab

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

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

**** p<0.0001, tocilizumab 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 TCZ 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 TCZ 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 TCZ 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 tocilizumab SC 162 mg weekly and tocilizumab 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 tocilizumab SC every week group (65.2%) versus the tocilizumab 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 tocilizumab in combination with DMARD/MTX or as monotherapy resulted in a highly statistically significant improvement in haemoglobin levels compared with placebo + MTX/DMARD ($p<0.0001$) at week 24. The greatest improvement was observed in patients with chronic anaemia associated with RA; mean haemoglobin 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 tocilizumab administration. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range.

MTX naïve, Early RA

Study VI, 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). This study evaluated the efficacy of IV tocilizumab 4 or 8 mg/kg every 4 weeks/MTX combination therapy, IV tocilizumab 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 < 2.6) at week 24. A significantly higher proportion of patients in the tocilizumab 8 mg/kg + MTX and tocilizumab monotherapy groups met the primary endpoint compared with MTX alone. The tocilizumab 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 tocilizumab 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 tocilizumab groups. The results from study VI are shown in Table 7.

Table 7: Efficacy Results for Study VI (WA19926) on MTX-naïve, early RA patients

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

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)

Monotherapy: tocilizumab 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 tocilizumab arm received an intravenous (IV) infusion of tocilizumab (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 tocilizumab 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 8).

Table 8: Efficacy Results for Study WA 19924

	ADA + Placebo (IV) N = 162	TCZ + 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 (%)	18 (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

Polyarticular Juvenile Idiopathic Arthritis

The efficacy of intravenous tocilizumab 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 tocilizumab 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 tocilizumab at 8 mg/kg for 4 doses. Patients < 30 kg were randomized 1:1 to receive either tocilizumab 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 tocilizumab (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 TCZ-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	TCZ 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, tocilizuma*b *vs. placebo*

Systemic Juvenile Idiopathic Arthritis

The efficacy of intravenous tocilizumab 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 (TCZ:placebo = 2:1) to one of two treatment groups, 75 patients received tocilizumab infusions every two weeks either 8 mg/kg for patients ≥30kg or 12 mg/kg for patients < 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 TCZ 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	TCZ 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, tocilizuma*b *vs. placebo*

Systemic Features

In those patients treated with tocilizumab, 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 tocilizumab 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 tocilizumab treated patients at week 12 in comparison to placebo patients. The adjusted mean change in the

pain VAS after 12 weeks of tocilizumab 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 tocilizumab patients receiving oral corticosteroids at baseline, 8 placebo and 48 tocilizumab patients achieved a JIA ACR70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) tocilizumab 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 tocilizumab 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 tocilizumab had a haemoglobin < 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 < LLN at baseline (p<0.0001). Forty four (88%) tocilizumab 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 tocilizumab 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 tocilizumab administration.

3.2 Pharmacokinetic Properties

Rheumatoid Arthritis

Intravenous Administration:

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1793 rheumatoid arthritis patients treated with a one hour infusion of 4 and 8 mg/kg every 4 weeks for 24 weeks.

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

concentration (C_{max}) increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 2.7 and 6.5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The following parameters are valid for a dose of 8 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 mcg•h/mL, 9.74 ± 10.5 mcg/mL, and 183 ± 85.6 mcg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 mcg•h/mL, 19.0 ± 12.0 mcg/mL, and 269 ± 57 mcg/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (*see section 2.2 Dosage and Administration).*

The following parameters are valid for a dose of 4 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800 mcg•h/mL, 1.49 ± 2.13 mcg/mL, and 88.3 ± 41.4 mcg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{min} (1.96). Steady-state was reached following the first administration for C_{max} and AUC, respectively, and after 16 weeks for C_{min}.

Subcutaneous Administration:

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

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

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

<u>Polyarticular Juvenile Idiopathic Arthritis</u>

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

The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight ≥ 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks},

C_{max} and C_{min} of tocilizumab were 29500 ± 8660 mcg•h/mL, 182 ± 37 mcg/mL and 7.49 ± 8.2 mcg/mL, respectively.

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

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{min} for 10 mg/kg (BW < 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 tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with systemic juvenile idiopathic arthritis treated with 8 mg/kg (patients with a body weight ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg), given every 2 weeks. The predicted mean (± SD) AUC_{2weeks}, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 mcg•h/mL, 245 ±57.2 mcg/mL and 57.5 ± 23.3 mcg/mL, respectively. The accumulation ratio for C_{min} (week12/week2) was 3.2 ± 1.3. The tocilizumab C_{min} was stabilized after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

3.2.1 Absorption

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

3.2.2 Distribution

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

In paediatric 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 paediatric 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 Metabolism

No text.

3.2.4 Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in rheumatoid arthritis patients, 5.8 mL/h in paediatric patients with polyarticular juvenile idiopathic arthritis and 7.1 mL/h in paediatric patients with systemic juvenile idiopathic arthritis. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab

concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab is concentration-dependent in rheumatoid arthritis. 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.

The $t_{1/2}$ of tocilizumab in children with pJIA is up to 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady state.

The $t_{1/2}$ of tocilizumab in children with sJIA 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 < 30 kg) at Week 12.

3.2.5 Pharmacokinetics in Special Populations

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.

Most of the patients in the rheumatoid arthritis population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ≥ 50 mL/min) did not impact the pharmacokinetics of tocilizumab. No dose adjustment is required in patients with mild renal impairment.

Other special populations

Population pharmacokinetic analyses in adult rheumatoid arthritis patients showed that age, gender and race did not affect pharmacokinetics of tocilizumab. No dose adjustment is necessary for these demographic factors.

3.3 Preclinical Safety

3.3.1 Carcinogenicity

A carcinogenicity study of tocilizumab 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 tocilizumab. 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 Mutagenicity

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

3.3.3 Impairment of Fertility

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

3.3.4 Teratogenicity

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

3.3.5 Other

In an embryo-foetal toxicity study conducted in cynomolgus monkeys a slight increase of abortion/embryo-foetal death was observed with high systemic cumulative exposure (>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 tocilizumab. Although IL-6 does not seem to be a critical cytokine for either foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to tocilizumab cannot be excluded.

Transfer of a murine analogue of tocilizumab 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 tocilizumab in the cynomolgus monkey does not suggest a difference between IV and SC routes of administration.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Intravenous tocilizumab:

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 tocilizumab 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 tocilizumab:

The medicine should not be used after the expiry date shown on the PFS and the pack. Store the PFS in a refrigerator at a temperature of 2-8°C (36-46°F). Do not freeze, keep in carton to protect from light, and keep dry.

4.2 Special Instructions for Use, Handling and Disposal

Intravenous tocilizumab:

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.

Rheumatoid Arthritis:

From a 100 mL infusion bag, withdraw a volume of 0.9% Sodium Chloride solution equal to the volume of the tocilizumab solution required for the patient's dose. Withdraw the required amount of tocilizumab (0.4 mL/kg) under aseptic conditions and dilute to a calculated tocilizumab 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 and sJIA Patients ≥ 30 kg:

From a 100 mL infusion bag, withdraw a volume of 0.9% Sodium Chloride solution equal to the volume of the tocilizumab solution required for the patient's dose. Withdraw the required amount of tocilizumab (0.4 mL/kg) under aseptic conditions and dilute to a calculated tocilizumab 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 < 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 tocilizumab under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

sJIA Patients < 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 tocilizumab under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

Subcutaneous tocilizumab:

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:

- Syringes should never be reused.
- Place all used syringes 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.

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

Vials 80 mg/4 ml	1, 4
Vials 200 mg/10 ml	1, 4
Vials 400 mg/20 ml	1, 4
Pre-filled syringes 162 mg/0.9 ml	1, 4

Medicine: keep out of reach of children

Current at March 2014

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