

PACK INSERT FOR MALAYSIA

Actemra® 162mg/0.9ml

Solution for injection in a pre-filled syringe

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) IgG₁ subclass.

ATC Code: L04AC07.

1.2 Type of Dosage Form

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

Subcutaneous (SC) injection.

1.4 Sterile / Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

Active ingredient: tocilizumab.

Excipients: L-histidine, L-histidine monohydrochloride monohydrate, L-arginine hydrochloride, L-methionine, polysorbate 80 and water for injection.

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.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Rheumatoid Arthritis (RA)

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 reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Giant Cell Arteritis (GCA)

Tocilizumab is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Tocilizumab in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Systemic Juvenile Idiopathic Arthritis (sJIA)

Tocilizumab is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

Tocilizumab can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) 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 SC injection.

For adult patients with GCA, tocilizumab is administered as a SC injection.

For patients with pJIA, tocilizumab is administered as a SC injection.

For patients with sJIA, tocilizumab is administered as a SC injection.

Tocilizumab SC formulation is not intended for intravenous administration.

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. 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 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.

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, General and 2.6 Undesirable Effects).

Rheumatoid Arthritis

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.

Giant Cell Arteritis (GCA)

The recommended dose is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. Tocilizumab can be used alone following discontinuation of glucocorticoids. Tocilizumab monotherapy should not be used for the treatment of acute relapses (see section 2.4 Warning and Precaution). Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

In the event of patients experiencing a relapse of GCA during the course of tocilizumab therapy, the treating physician should consider re-introducing and/or escalating the dose of concomitant glucocorticoids (or restarting glucocorticoid therapy if it has been discontinued) according to best medical judgement/treatment guidelines.

Dose Modification Recommendations for RA and GCA (see section 2.4.1 Warnings and Precautions, General):

- Liver enzyme abnormalities

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if 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 has 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)

In patients not previously treated with Tocilizumab, initiation is not recommended in patients with an absolute neutrophil count (ANC) below $2 \times 10^9/L$.

Lab Value (cells x 10 ⁹ /L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt tocilizumab dosing. 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 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)

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.

Subcutaneous Dosing Regimen:

The recommended dose of SC tocilizumab for patients with pJIA is:

- 162 mg once every three weeks for patients below 30 kg,
- 162 mg once every two weeks for patients \geq 30 kg

The PFS+NSD can be used to treat paediatric patients of all approved ages.

Systemic Juvenile Idiopathic Arthritis (sJIA)

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.

The recommended dose of SC tocilizumab for patients with sJIA is:

- 162 mg once every two weeks for patients below 30 kg,
- 162 mg once every week for patients \geq 30 kg
- Patients must have a minimum body weight of 10kg when receiving Actemra subcutaneously.

The PFS+NSD can be used to treat paediatric patients of all approved ages.

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 and GCA (also see section 2.4.1 Warnings and Precautions, General). 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

Pediatric use: The safety and efficacy in patients aged less than 2 years in pJIA has not been established. The safety and efficacy in patients aged less than 2 years in sJIA has not been established.

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 3.2.5 Pharmacokinetics in Special Populations). Tocilizumab has not been studied in patients with 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

Actemra is contraindicated in patients with a known hypersensitivity to tocilizumab or to any of the excipients.

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 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 immunosuppressive agents, such as tocilizumab, 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 or 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 tocilizumab. 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, all 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 paediatric or elderly patients, 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 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 treatment 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.Undesirable Effects, Clinical Trials).

Hepatotoxicity

Mild and moderate elevations of hepatic transaminases have been observed with tocilizumab 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 tocilizumab.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (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 tocilizumab. Cases of liver failure resulting in liver transplantation have been reported.

Caution should be exercised when considering initiation of tocilizumab 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.

In RA, GCA,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 tocilizumab 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 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.

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.Undesirable Effects, Clinical Trials).

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

In RA and GCA, 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 administration 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 Undesirable Effects, Clinical Trials).

Caution should be exercised when considering initiation of tocilizumab treatment in patients with a platelet count below $100 \times 10^9/\mu\text{L}$. In patients with a platelet count below $50 \times 10^9/\mu\text{L}$ treatment is not recommended.

In RA and GCA, 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 administration 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 Undesirable Effects, Clinical Trials).

In patients treated with tocilizumab, 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.

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.

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.

2.5 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 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.

2.5.3 Paediatric Use

(See section 2.2.1 Special Dosage Instructions.)

2.5.4 Geriatric Use

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

2.5.5 Renal Impairment

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

2.5.6 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

The safety profile in this section comes from 4510 patients exposed to tocilizumab 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 tocilizumab 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) or uncommon ($\geq 1/1000$ to $< 1/100$).

Table 1 Summary of ADRs occurring in patients treated with tocilizumab

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	Total bilirubin increased

Vascular disorders		increased	
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 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.

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 infections have also been reported.

Gastrointestinal Perforation

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 studied 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 (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 tocilizumab 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 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.

Giant Cell Arteritis

The safety of subcutaneous tocilizumab has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the tocilizumab all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. 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).

Infections

The rate of infection/serious infection events was balanced between the tocilizumab weekly group (200.2/9.7 events per 100 patient years) versus placebo plus 26 weeks prednisone taper (156.0/4.2 events per 100 patient years) and placebo plus 52 weeks taper (210.2/12.5 events per 100 patient years) groups.

Polyarticular Juvenile Idiopathic Arthritis

The safety profile of tocilizumab was studied in 240 paediatric patients with pJIA. In Study WA19977, 188 patients (2 to 17 years of age) were treated with IV tocilizumab and in Study WA28117, 52 patients (1 to 17 years of age) were treated with SC tocilizumab. The total patient exposure to tocilizumab in the pJIA all exposure population was 184.4 patient years for IV tocilizumab and 50.4 patient years for SC tocilizumab. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of tocilizumab with the exception of ISRs (see Table 1). A higher frequency of ISRs was experienced by pJIA patients following SC tocilizumab injections compared to adult RA patients (see Undesirable Effects section).

Infections

Infections are the most commonly observed events in pJIA. The rate of infections in the pJIA IV 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 below 30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing \geq 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 below 30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing \geq 30 kg, treated with 8

mg/kg tocilizumab (7.6%). The rate of infection in pJIA patients treated with SC tocilizumab was comparable with pJIA patients treated with IV tocilizumab.

Infusion Reactions

In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion with IV tocilizumab. 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.

Injection Site Reactions

A total of 28.8% (15/52) pJIA patients experienced ISRs to SC tocilizumab. These ISRs occurred in 44% of patients $>$ 30 kg compared to 14.8% of patients below 30 kg. The most common ISRs were injection site erythema, swelling, hematoma, pain and pruritis. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

Immunogenicity

Across the two studies in pJIA patients, a total of four patients (0.5% [1/188] in the IV Study WA19977 and 5.8% [3/52] in the SC Study WA28117) developed positive neutralizing anti-tocilizumab antibodies without developing a serious or clinically significant hypersensitivity reaction. Of these 4 patients, 2 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed.

Systemic Juvenile Idiopathic Arthritis

The safety profile of tocilizumab in sJIA was studied in 163 paediatric patients. In Study WA18221 (12-week trial and long term extension), 112 patients (2 to 17 years of age) were treated with IV tocilizumab and in Study WA28118 (52-week trial), 51 patients (1 to 17 years of age) were treated with SC tocilizumab. 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 (Study WA18221), the rate of all infections in the IV tocilizumab group was 344.7 per 100 patient-years and 287.0 per 100 patient-years in the placebo group. In the 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 (Study WA18221), the rate of serious infections in the IV tocilizumab group was 11.5 per 100 patient years. In the 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.

The rate of infection in sJIA patients treated with SC tocilizumab was comparable to sJIA patients treated with IV tocilizumab.

Injection Reactions

For sJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion with IV tocilizumab. In the 12 week controlled trial (Study WA18221), 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 IV 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 IV tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (below 1%) treated with IV tocilizumab during the controlled and open-label parts of the clinical trial.

Injection Site Reactions (ISRs)

In Study WA28118, a total of 41.2% (21/51) sJIA patients experienced ISRs to SC tocilizumab. The most common ISRs were erythema, pruritus, pain, and swelling at the injection site. The majority of ISRs reported were Grade 1 events and all ISRs reported were non-serious and none of the ISRs required patient withdrawal from treatment or dose interruption.

Immunogenicity

In Study WA18221, 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. In Study WA28118, 46 of the 51 (90.2%) patients tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post baseline.

Laboratory Abnormalities

Haematology abnormalities:

Neutrophils

There was no clear relationship between decreases in neutrophils below $1 \times 10^9/L$ 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 $1 \times 10^9/\text{L}$ occurred in 3.4% of patients on tocilizumab 8 mg/kg+DMARD compared to below 0.1% of patients on placebo+DMARD. Approximately half of the instances of ANC below $1 \times 10^9/\text{L}$ occurred within 8 weeks of starting therapy. Decreases below $0.5 \times 10^9/\text{L}$ were reported in 0.3% patients receiving tocilizumab 8 mg/kg +DMARD (see sections 2.2 Dosage and Administration, 2.4.1 Warnings and Precautions).

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 $1 \times 10^9/\text{L}$ occurred in 2.9% of patients on tocilizumab 162 mg SC weekly.

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, a decrease in neutrophil count below $1 \times 10^9/\text{L}$ occurred in 4% of patients in the tocilizumab SC weekly group. This was not observed in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below $1 \times 10^9/\text{L}$ occurred in 3.7% of patients treated with IV tocilizumab and 15.4% of patients treated with SC tocilizumab.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), a decrease in neutrophil counts below $1 \times 10^9/\text{L}$ occurred in 7% of patients in the IV tocilizumab group, and in none in the placebo group.

In the open-label extension study (WA18221), decreases in neutrophil counts below $1 \times 10^9/\text{L}$, occurred in 15% of the IV tocilizumab group

In the 52-week open-label trial (Study WA28118), neutrophil count decrease below $1 \times 10^9/\text{L}$ occurred in 23.5% of patients treated with SC tocilizumab

Platelets

Rheumatoid Arthritis

Intravenous Administration:

In the 6 month controlled trials decreases in platelet counts below $100 \times 10^3 / \mu\text{L}$ occurred in 1.7% of patients on tocilizumab 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).

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, none of the patients had a decrease in platelet count to $\leq 50 \times 10^3 / \mu\text{L}$.

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, one patient (1%, 1/100) in the tocilizumab SC weekly group had a single transient occurrence of decreased platelet count below $100 \times 10^3 / \mu\text{L}$ without associated bleeding events. A decrease in platelet count below $100 \times 10^3 / \mu\text{L}$ was not observed in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in platelet count to $\leq 50 \times 10^3 / \mu\text{L}$ occurred in 1% patients treated with IV tocilizumab, without associated bleeding events and in no patients treated with SC tocilizumab.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), 3% of patients in the placebo group and 1% in the IV tocilizumab group had a decrease in platelet count to $\leq 100 \times 10^3 / \mu\text{L}$.

In the open-label extension study (WA18221), decreases in platelet counts below $100 \times 10^3 / \mu\text{L}$ occurred in 3% of patients of the IV tocilizumab group, without associated bleeding events

In the 52-week open-label trial (Study WA28118), decreases in platelet counts below $100 \times 10^3 / \mu\text{L}$ occurred in 2% of patients treated with SC tocilizumab.

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 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 above 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, 2.4.1 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 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 above 3xULN compared with the *all control* population. This was observed in both tocilizumab treated patients and MTX monotherapy patients.

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

Subcutaneous Administration:

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

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, elevation in ALT ≥ 3 ULN occurred in 3% of patients in the tocilizumab SC weekly group compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 weeks prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the tocilizumab SC weekly group, compared to no patients in either of the placebo plus prednisone taper group.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST $\geq 3 \times$ ULN occurred in 3.7% and below 1% of patients treated with IV tocilizumab, and in 9.6% and 3.8% patients treated with SC tocilizumab, respectively.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), elevation in ALT or AST $\geq 3 \times$ ULN occurred in 5% and 3% of patients, respectively, in the IV tocilizumab group, and in 0% of placebo patients.

In the open-label extension study (WA18221), elevation in ALT or AST $\geq 3 \times$ ULN occurred in 12% and 4% of patients, respectively, in the IV tocilizumab group.

In the 52-week open-label trial (Study WA28118), elevation in ALT or AST $\geq 3 \times$ ULN occurred in 9.8% and 4.0% patients treated with SC tocilizumab, respectively

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 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.

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 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.

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, 29% of patients experienced elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 12% experiencing an increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the tocilizumab SC weekly group.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the IV tocilizumab Study WA19977, 3.4 % and 10.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during the study treatment, respectively. In the SC tocilizumab Study WA28117, 14.3% and 12.8% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), 13.4% and 33.3% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL, respectively.

In the open-label extension study (WA18221), 13.2% and 27.7% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL, respectively.

In the 52-week open-label trial (Study WA28118), 23.4% and 35.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL, respectively].

2.6.2 Post Marketing Experience

The following adverse drug reactions have been identified from post marketing experience with tocilizumab (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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	0.027 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 TCZ 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 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.

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 tocilizumab clearance in RA patients. In GCA patients, no effect of cumulative corticosteroid dose on tocilizumab exposure was observed.

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, cyclosporin, 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 ($t_{1/2}$), the effect of tocilizumab 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 tocilizumab in RA, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A and fibrinogen were observed. Increases in haemoglobin levels were observed, through tocilizumab 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 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 and GCA patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see section 2.4.1. Warnings and Precautions, General).

3.1.1 Mechanism of Action

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Tocilizumab 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 signalling. 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 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 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 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%						

Table 3 Cross-Study Comparison of DAS and EULAR 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 + DMA RD 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)	

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 open label extension studies of Studies I -IV.

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).

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 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
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 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 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 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	
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	TCZ 8 mg/kg + DMARD N=803	Placebo	TCZ 8 mg/kg +MTX N=170	Placebo 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 below 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)
ACR			
Week 24	ACR20, n (%)	216 (74.5)*	205 (70.2)
	ACR50, n (%)	165 (56.9)**	139 (47.6)
	ACR70, n (%)	112 (38.6)**	88 (30.1)
Week 52	ACR20, n (%)	195 (67.2)*	184 (63.0)
	ACR50, n (%)	162 (55.9)**	144 (49.3)
	ACR70, n (%)	125 (43.1)**	105 (36.0)
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
	Erosion Score	0.05**	0.15
	JSN	0.03	0.11
Radiographic Non-Progression n (%)	226 (83)‡	226 (82)‡	194 (73)
(change from baseline in mTSS of ≤0)			
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

^ap value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.

^bNon-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

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 [100]. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with TCZ 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 TCZ 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 TCZ 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 TCZ to ETA = 1.05; 95% CI = 0.77, 1.43).

Giant Cell Arteritis (GCA)

Study WA28119 was a randomized, multi-center, double-blind placebo-controlled Phase III superiority study conducted to assess the efficacy and safety of tocilizumab in patients with GCA.

Two hundred and fifty one (251) patients with new-onset or relapsing GCA were enrolled and assigned to one of four treatment arms. The study consisted of a 52-week blinded period (Part 1), followed by a 104-week open-label extension (Part 2). The purpose of the Part 2 is to describe the long term safety and maintenance of efficacy after 52 weeks of tocilizumab therapy, to explore the rate of relapse and the requirement for tocilizumab therapy beyond 52 weeks, and to gain insight into the potential long-term steroid-sparing effect of tocilizumab.

Two subcutaneous (SC) doses of tocilizumab (162 mg every week and 162 mg every other week) were compared to two different placebo control groups randomized 2:1:1.

All patients received background glucocorticoid (prednisone) therapy. Each of the tocilizumab-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen over 52 weeks designed to be more in keeping with standard practice.

The primary efficacy endpoint, assessed by the proportion of patients achieving steroid-free sustained remission at Week 52 on tocilizumab plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 11).

The key secondary efficacy endpoint, also based on the proportion of patients achieving sustained remission at Week 52, comparing tocilizumab plus 26 weeks prednisone taper with the longer placebo plus 52 weeks prednisone taper, was also met (Table 11).

A statistically significant superior treatment effect was seen in favour of tocilizumab over placebo in achieving steroid-free sustained remission at Week 52 on tocilizumab plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper and with placebo plus 52 weeks prednisone taper.

The percentage of patients achieving sustained remission at week 52 are shown in Table 11 below.

Secondary Endpoints

The assessment of the time to first GCA flare showed a significantly lower risk of flare for the tocilizumab SC weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the tocilizumab SC every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). Tocilizumab SC weekly dose also showed a clinically meaningful decrease in the risk for flare compared to placebo plus 26 weeks prednisone in patients who entered the trial with relapsing GCA as well as those with new-onset disease (Table 9).

Cumulative glucocorticoid dose

The cumulative prednisone dose at Week 52 was significantly lower in the two tocilizumab dose groups compared to the two placebo groups (Table 9). In a separate analysis of the patients who received escape prednisone to treat GCA flare during the first 52 weeks, the cumulative prednisone dose varied greatly. The median doses for escape patients in the tocilizumab weekly and every other weekly groups were 3129.75 mg and 3847 mg, respectively – both considerably lower than in the placebo plus 26 weeks and the placebo plus 52 weeks prednisone taper groups, 4023.5 mg and 5389.5 mg respectively.

Table 9: Efficacy Results from Study WA28119

	PBO + 26 weeks prednisone taper N=50	PBO + 52 weeks prednisone taper N=51	TCZ 162mg SC QW + 26 weeks prednisone taper N=100	TCZ 162 mg SC Q2W + 26 weeks prednisone taper N=49
Primary Endpoint				
Sustained remission (TCZ groups vs PBO+26)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	42%* (18.00, 66.00)	39.06%* (12.46 , 65.66)
Key Secondary Endpoint				
Sustained remission (TCZ groups vs PBO+52)				

Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	38.35%* (17.89 , 58.81)	35.41%** (10.41 ,60.41)
Other Secondary Endpoints				
Time to first GCA flare ¹ (TCZ groups vs PBO+26) HR (99% CI)	N/A	N/A	0.23* (0.11, 0.46)	0.28** (0.12, 0.66)
Time to first GCA flare ¹ (TCZ groups vs PBO+52) HR (99% CI)	N/A	N/A	0.39** (0.18, 0.82)	0.48 (0.20, 1.16)
Time to first GCA flare ¹ (Relapsing patients; TCZ groups vs PBO +26) HR (99% CI)	N/A	N/A	0.23*** (0.09, 0.61)	0.42 (0.14, 1.28)
Time to first GCA flare ¹ (Relapsing patients; TCZ groups vs PBO + 52) HR (99% CI)	N/A	N/A	0.36 (0.13, 1.00)	0.67 (0.21,2.10)
Time to first GCA flare ¹ (New-onset patients; TCZ groups vs PBO +26) HR (99% CI)	N/A	N/A	0.25*** (0.09, 0.70)	0.20*** (0.05, 0.76)
Time to first GCA flare ¹ (New-onset patients; TCZ groups vs PBO + 52) HR (99% CI)	N/A	N/A	0.44 (0.14, 1.32)	0.35 (0.09, 1.42)
Cumulative glucocorticoid dose (mg)				
median at Week 52 (TCZ groups vs PBO+26 ²)	3296.00	N/A	1862.00*	1862.00**
median at Week 52 (TCZ groups vs PBO +52 ²)	N/A	3817.50	1862.00*	1862.00*
Exploratory Endpoints				
Annualized relapse rate, Week 52 [§]	1.74	1.30	0.41	0.67
Mean (SD)	(2.18)	(1.84)	(0.78)	(1.10)

*p<0.0001

**p<0.005 (threshold for significance for primary and key secondary tests of superiority)

***descriptive p value <0.005

¹analysis of the time (in days) between clinical remission and first disease flare

²p-values are determined using a Van Elteren analysis for non-parametric data

§ statistical analyses has not been performed

N/A= Not applicable

HR = Hazard Ratio; CI = Confidence Interval

TCZ: Tocilizumab

PBO: Placebo

QW: every week dose

Q2W: every other week dose

Quality of Life Outcomes

In study WA28119, the SF-36 results were separated into the physical and mental component summary scores (PCS and MCS, respectively). The PCS mean change from baseline to week 52 was higher (showing more improvement) in the tocilizumab weekly and every other weekly dose groups [4.10, 2.76, respectively] than in the two placebo (PBO) groups [PBO plus 26 weeks; -0.28, PBO plus 52 weeks; -1.49], although only the comparison between tocilizumab weekly plus 26 weeks prednisone taper group and placebo plus 52 weeks prednisone taper group (5.59, 99% CI: 0.86 10.32) showed a statistically significant difference (p=0.0024). For MCS, the mean change from baseline to week 52 for both tocilizumab weekly and every other weekly dose groups [7.28, 6.12, respectively] were higher than the placebo plus 52 weeks prednisone taper group [2.84] (although the differences were not statistically significant [p=0.0252 for weekly, p=0.1468 for every other weekly]) and similar to the placebo plus 26 weeks prednisone taper group [6.67].

The Patient's Global Assessment of disease activity was assessed on a 0-100mm Visual Analogue Scale (VAS). The mean change in Patient's global VAS from baseline at week 52 was lower (showing greater improvement) in the tocilizumab weekly and every other weekly dose groups [-19.0, -25.3, respectively] than in both placebo groups [PBO plus 26 weeks; -3.4, PBO plus 52 weeks; -7.2], although only the tocilizumab every other weekly plus 26 weeks prednisone taper group showed a statistically significance difference compared to placebo [PBO plus 26 weeks taper p=0.0059, and PBO plus 52 week taper p=0.0081].

FACIT-Fatigue change from baseline to Week 52 scores were calculated for all groups. The mean [SD] change scores were as follows: tocilizumab weekly plus 26 weeks 5.61 [10.115], tocilizumab every other weekly plus 26 weeks 1.81 [8.836], PBO plus 26 weeks 0.26 [10.702], and PBO plus 52 weeks -1.63 [6.753].

Change in EQ5D scores from baseline to week 52 were tocilizumab weekly plus 26 weeks 0.10 [0.198], tocilizumab every other weekly plus 26 weeks 0.05 [0.215], PBO plus 26 weeks 0.07 [0.293], and PBO plus 52 weeks -0.02 [0.159].

Higher scores signal improvement in both FACIT-Fatigue and EQ5D.

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 below 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 10 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, tocilizumab vs. placebo

A 52-week, open-label, multi-center, PK-PD and safety study (WA28117) was conducted in paediatric patients with pJIA, aged 1 to 17 years old, to determine the appropriate subcutaneous dose of tocilizumab (TCZ) that achieved comparable PK/PD and safety profiles to the IV regimen.

Eligible patients received tocilizumab dosed according to body weight (BW), with patients weighing ≥30 kg (n = 25) dosed with 162 mg of tocilizumab every 2 weeks (Q2W) and patients weighing below 30 kg (n = 27) dosed with 162 mg of TCZ every 3 weeks (Q3W) for 52 weeks. Of these 52 patients, 37 (71%) were naïve to tocilizumab and 15 (29%) had been receiving IV TCZ and switched to SC TCZ at baseline.

The SC TCZ regimens of 162 mg Q3W for patients weighing below 30 kg and of 162 mg Q2W for patients weighing ≥ 30 kg, respectively provided PK exposure and PD responses to support efficacy and safety outcomes similar to those achieved with the approved IV TCZ regimens for pJIA.

Exploratory efficacy results showed that SC tocilizumab improved median Juvenile Arthritis Disease Activity Score (JADAS)-71 for TCZ naïve patients and maintained the median JADAS-71 for patients who switched from IV to SC TCZ treatment over the entire course of the study for patients in both body weight groups (below 30 kg and ≥ 30 kg).

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 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 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 11 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%

* $p<0.0001$, tocilizumab 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 $\geq 37.5^{\circ}\text{C}$ 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 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 open label extension.

Laboratory Parameters

Fifty out of seventy five (67%) patients treated with tocilizumab 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%) tocilizumab patients with decreased haemoglobin at baseline had an increase in their haemoglobin by $\geq 10\text{ g/L}$ 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.

A Phase I, multi-centre, open-label, single arm study (NP25737) to evaluate the PK, safety and exploratory PD and efficacy of tocilizumab 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 tocilizumab 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 $AUC_{2\text{weeks}}$) of TCZ 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-tocilizumab antibodies after the event. However, due to the small sample size, the low number of events and confounding factors, conclusions could not be drawn.

Exploratory efficacy results showed that tocilizumab improved the median JADAS-71 score over the course of the study for all patients. The observed PD responses in sIL6R, CRP, and ESR were also consistent with the pivotal Phase III study.

A 52-week, open-label, multi-centre, PK/PD and safety study (WA28118) was conducted in paediatric patients with sJIA, aged 1 to 17 years, to determine the appropriate SC dose of TCZ that achieved comparable PK/PD and safety profiles to the IV regimen.

Eligible patients received TCZ dosed according to body weight (BW), with patients weighing $\geq 30\text{ kg}$ ($n = 26$) dosed with 162 mg of TCZ every week (QW) and patients weighing below 30 kg ($n = 25$) dosed with 162 mg of TCZ every 10 days (Q10D; $n=8$) or every 2 weeks (Q2W; $n=17$) for 52 weeks. Of these 51 patients, 26 (51%) were naïve to TCZ and 25 (49%) had been receiving IV TCZ and switched to SC TCZ at baseline.

Exploratory efficacy results showed that SC tocilizumab improved all exploratory efficacy parameters including Juvenile Arthritis Disease Activity Score (JADAS)-71, for TCZ naïve patients and maintained all exploratory efficacy parameters for patients who switched from IV to SC TCZ treatment over the entire course of the study for patients in both body weight groups (below 30 kg and $\geq 30\text{ kg}$).

3.2 Pharmacokinetic Properties

PK of tocilizumab is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of tocilizumab elimination leads to an increase in exposure that is more than

dose-proportional. The pharmacokinetic parameters of tocilizumab do not change with time. Due to the dependence of total clearance on tocilizumab serum concentrations, the half-life of tocilizumab 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 AUC_{tr} .

Table 12 Predicted mean \pm SD PK parameters at steady-state after IV and SC dosing in RA

TCZ PK Parameter	IV		SC	
	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_{tr}^*	1.09	1.32	2.67	6.32

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

At high serum concentrations, when total clearance of tocilizumab 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 dose-proportionally between doses of 4 and 8 mg/kg IV every 4 weeks, a greater than dose-proportional 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_{tr} 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 tocilizumab. When given IV on a mg/kg basis, individuals with body weight $\geq 100\text{ kg}$ are predicted to have mean steady-state exposures higher than mean values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients $\geq 100\text{ kg}$ (see section 2.2 Dosage and Administration). Due to the flat dosing employed for SC administration of tocilizumab, no modifications are necessary by this dosing route.

Giant Cell Arteritis (GCA)

The pharmacokinetics of tocilizumab in GCA patients were determined using a popPK model from an analysis dataset composed of 149 GCA patients treated with 162 mg SC every week or with 162 mg SC every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients.

Table 13: Predicted mean \pm SD PK parameters at steady-state after SC dosing in GCA

TCZ PK Parameter	SC	
	162 mg Q2W	162 mg QW
C _{max} (mcg/mL)	19.3 ± 12.8	73 ± 30.4
C _{trough} (mcg/mL)	11.1 ± 10.3	68.1± 29.5
C _{mean} (mcg/mL)	16.2 ± 11.8	71.3 ± 30.1
Accumulation C _{max}	2.26	8.88
Accumulation C _{trough}	5.61	9.59
Accumulation C _{mean} or AUC _T	2.81	10.91
*		

*T = 2 week or 1 week for the two SC regimens, respectively

The steady-state profile following the tocilizumab weekly dose was almost flat, with very little fluctuations between trough and peak values, while there were substantial fluctuations for the tocilizumab every other week dose. Approximately 90% of the steady-state (AUC_T) was reached by Week 14 in the every other weekly and Week 17 in the weekly dose groups.

Polyarticular Juvenile Idiopathic Arthritis

The pharmacokinetics of tocilizumab in pJIA patients was characterized by a population pharmacokinetic analysis which included 237 patients who were treated with 8 mg/kg IV every 4 weeks (patients weighing ≥ 30 kg), 10 mg/kg IV every 4 weeks (patients weighing below 30 kg), 162 mg SC every 2 weeks (patients weighing ≥ 30 kg), or 162 mg SC every 3 weeks (patients weighing below 30 kg).

Table 14. Predicted mean ± SD PK parameters at steady-state after IV or SC dosing in pJIA

TCZ PK Parameter	IV 8 mg/kg Q4W ≥ 30 kg	IV 10 mg/kg Q4W below 30 kg	SC 162 mg Q2W ≥ 30 kg	SC 162 mg Q3W below 30 kg
C _{max} (μg/mL)	183 ± 42.3	168 ± 24.8	29.4 ± 13.5	75.5 ± 24.1
C _{trough} (μg/mL)	6.55 ± 7.93	1.47 ± 2.44	11.8 ± 7.08	18.4 ± 12.9
C _{mean} (μg/mL)	42.2 ± 13.4	31.6 ± 7.84	21.7 ± 10.4	45.5 ± 19.8
Accumulation C _{max}	1.04	1.01	1.72	1.32
Accumulation C _{trough}	2.22	1.43	3.58	2.08
Accumulation C _{mean} or AUC _T *	1.16	1.05	2.04	1.46

*T = 4 weeks for IV regimens, 2 week or 3 week for the two SC regimens, respectively

After IV dosing, approximately 90% of the steady-state was reached by Week 12 for the 10 mg/kg (BW < 30 kg), and by Week 16 for the 8 mg/kg (BW ≥ 30 kg) dose. After SC dosing, approximately 90% of the steady-state was reached by Week 12 for both the 162 mg SC Q2W and Q3W regimens.

Systemic Juvenile Idiopathic Arthritis

The pharmacokinetics of tocilizumab in sJIA patients was characterized by a population pharmacokinetic analysis which included 140 patients who were treated with 8 mg/kg IV every 2 weeks (patients weighing ≥ 30 kg), 12 mg/kg IV every 2 weeks (patients weighing below 30 kg), 162 mg SC every week (patients weighing ≥ 30 kg), 162 mg SC every 10 days or every 2 weeks (patients weighing below 30 kg).

Table 15. Predicted mean ± SD PK parameters at steady-state after IV or SC dosing in sJIA

TCZ PK Parameter	IV 8 mg/kg Q2W ≥ 30 kg	IV 12 mg/kg Q2W below 30 kg	SC 162 mg QW ≥ 30 kg	SC 162 mg Q2W below 30 kg
C _{max} (μg/mL)	256 ± 60.8	274 ± 63.8	99.8 ± 46.2	134 ± 58.6
C _{trough} (μg/mL)	69.7 ± 29.1	68.4 ± 30.0	79.2 ± 35.6	65.9 ± 31.3
C _{mean} (μg/mL)	119 ± 36.0	123 ± 36.0	91.3 ± 40.4	101 ± 43.2
Accumulation C _{max}	1.42	1.37	3.66	1.88
Accumulation C _{trough}	3.20	3.41	4.39	3.21

Accumulation C _{mean} or AUC _T *	2.01	1.95	4.28	2.27
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*T = 2 weeks for IV regimens, 1 week or 2 week for the two SC regimens, respectively

After IV dosing, approximately 90% of the steady-state was reached by Week 8 for both the 12 mg/kg and 8 mg/kg Q2W regimens. After SC dosing, approximately 90% of the steady-state was reached by Week 12 for both the 162 mg QW and Q2W regimens.

The pharmacokinetics of tocilizumab 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 tocilizumab given every 2 weeks.

3.2.1 Absorption

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

In GCA patients, the median values of Tmax were 3 days after the tocilizumab weekly dose and 4.5 days after the tocilizumab every other week dose.

Following SC dosing in pJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in pJIA patients was 96%.

Following SC dosing in sJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in sJIA patients was 95%.

3.2.2 Distribution

In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L resulting in a volume of distribution at a steady state of 7.46 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 1.87 L, the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at steady state of 4.01 L.

3.2.3 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 RA patients, 6.7 mL/h in GCA patients, 5.8mL/h in paediatric patients with polyarticular juvenile idiopathic arthritis and 5.7 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. Due to dependence of total clearance on tocilizumab serum concentrations, t_{1/2} of tocilizumab is also concentration-dependent and can only be calculated at a given serum concentration level.

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 tocilizumab is dominated by linear clearance, a terminal t_{1/2} of approximately 21.5 days was derived from the population parameter estimates.

In GCA patients, at steady state, the effective t_{1/2} of tocilizumab varied between 18.3 and 18.9 days for 162 mg weekly regimen, and between 4.2 and 7.9 days for 162 mg every other weekly regimen. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, an effective t_{1/2} of approximately 32 days was derived from the population parameter estimates.

After subcutaneous administration, the effective t_{1/2} of tocilizumab in pJIA patients is up to 10 days for the two body weight categories (Q2W regimen for body weight ≥ 30 kg or Q3W regimen for body weight below< 30 kg) during a dosing interval at steady state.

Following subcutaneous administration, the effective t_{1/2} of tocilizumab in sJIA patients is up to 14 days for both the 162 mg QW and Q2W regimens during a dosing interval at steady state.

3.2.3 Pharmacokinetics in Special Populations

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been 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 RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab.

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 tocilizumab exposure was noted in these patients.

No dose adjustment is required in patients with mild or moderate renal impairment.

Other special populations

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

3.3 Nonclinical 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 Genotoxicity

Standard genotoxicity studies with tocilizumab 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 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 Reproductive Toxicity

When tocilizumab 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-fetal 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

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.

Once removed from the refrigerator, the PFS can be stored up to 2 weeks at or below 30°C (86°F). The PFS must be kept in the carton to protect from light and keep dry.

4.2 Special Instructions for Use, Handling and Disposal

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

Pre-filled syringe 162mg

1, 4

Medicine: keep out of reach of children

MYActemraSC20220623/CDS22.0

Revision date: June 2022

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany

Instructions for Use ACTEMRA® (AC-TEM-RA) (tocilizumab)

Injection, For Subcutaneou Use

Single-dose Prefilled Syringe

Read and follow the Instructions for Use that come with your ACTEMRA prefilled syringe before you start using it and each time you get a prescription refill. Before you use ACTEMRA prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it.

- Do not remove the needle cap until you are ready to inject ACTEMRA.
- Do not try to take apart the syringe at any time.
- Do not reuse the same syringe.

Parts of your ACTEMRA Prefilled Syringe (See Figure A).

Pre-filled syringe parts

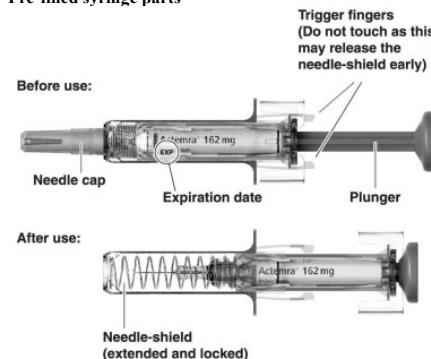


Figure A

Supplies needed for your ACTEMRA Prefilled Syringe Injection (See Figure B):

- ACTEMRA prefilled syringe
- alcohol pad
- sterile cotton ball or gauze
- puncture-resistant container or sharps container for safe disposal of needle cap and used syringes (See Step 4 "Dispose of the syringe")

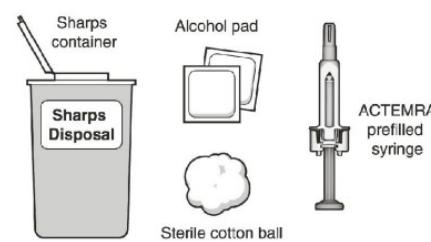


Figure B

Step 1. Preparing for an ACTEMRA Injection

Find a comfortable space with a clean, flat, working surface.

- Take the box containing the syringe out of the refrigerator and open the box. Do not touch the trigger fingers on the syringes as this may damage the syringe.
- Remove 1 single-use ACTEMRA prefilled syringe from the box and let it warm up for 30 minutes to allow it to reach room temperature. If the syringe does not reach room temperature, this could cause your injection to feel uncomfortable and make it difficult to push the plunger in.
- Do not speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.
- Check the expiration date on the ACTEMRA prefilled syringe (See Figure A). Do not use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed safely dispose of the syringe in the sharps container and get a new one.

Do not remove the needle cap while allowing your ACTEMRA prefilled syringe to reach room temperature.

- Keep your unused syringes in the original carton and keep in the refrigerator at 2°C to 8°C. **Do not freeze.**
- Once removed from the refrigerator, your prefilled syringe can be stored up to 2 weeks at or below 30°C (86°F). Your prefilled syringe must always be kept in the original carton in order to protect from light and moisture.
- Hold your ACTEMRA prefilled syringe with the covered needle pointing down (See Figure C).

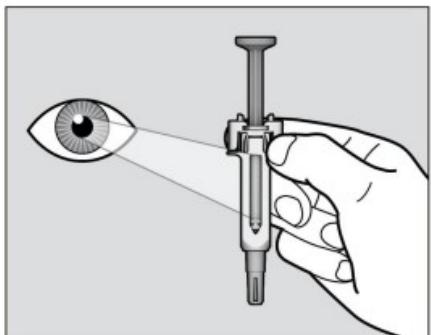


Figure C

- Check the liquid in the ACTEMRA prefilled syringe. It should be clear and colorless to pale yellow. Do not inject ACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the syringe in a sharps container and get a new one.
- Wash your hands well with soap and water.

Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh and your abdomen except for the 2-inch area around your navel are the recommended injection sites (See Figure D).
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself (See Figure D).

Rotate Injection Site

- Choose a different injection site for each new injection at least 1 inch from the last area you injected.
- Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

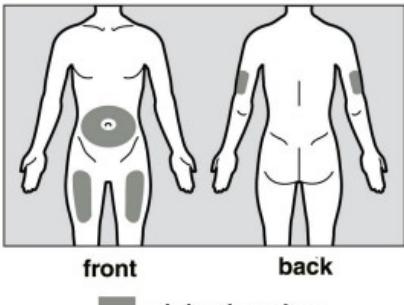


Figure D

Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Step 3. Inject ACTEMRA

- Hold the ACTEMRA prefilled syringe with 1 hand and pull the needle cap straight off with your other hand (See Figure E). **Do not** hold the plunger while you remove the needle cap. If you cannot remove the needle cap you should ask a caregiver for help or contact your healthcare provider.

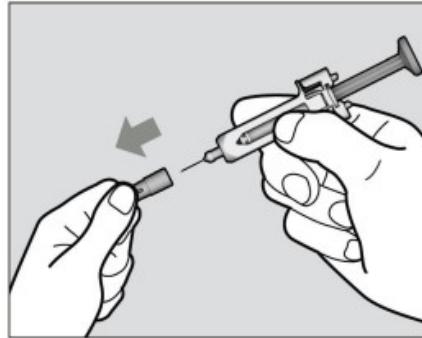


Figure E

- Throw away the needle cap in a sharps container.
- There may be a small air bubble in the ACTEMRA prefilled syringe. You do not need to remove it.
- You may see a drop of liquid at the end of the needle. This is normal and will not affect your dose.
- **Do not** touch the needle or let it touch any surfaces.
- **Do not** use the prefilled syringe if it is dropped.
- If it is not used within 5 minutes of needle cap removal, the syringe should be disposed of in the puncture resistant container or sharps container and a new syringe should be used.
- Never reattach the needle cap after removal.
- Hold the ACTEMRA prefilled syringe in 1 hand between the thumb and index finger (See Figure F).

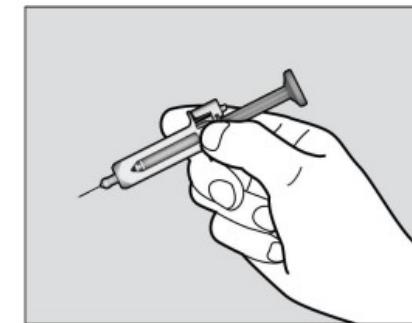


Figure F

- **Do not** pull back on the plunger of the syringe.
- Use your other hand and gently pinch the area of skin you cleaned. Hold the pinched skin firmly. Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.
- **Do not** hold or push on the plunger while inserting the needle into the skin.
- Use a quick, dart-like motion to insert the needle all the way into the pinched skin at an angle between 45° to 90° (See Figure G). It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.

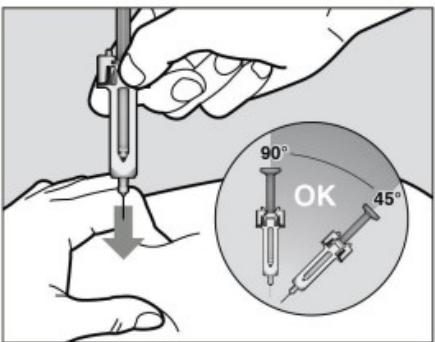


Figure G

- Keep the syringe in position and let go of the pinch of skin.
- Slowly inject all of the medicine by gently pushing the plunger all the way down (See **Figure H**). You must press the plunger all the way down to get the full dose of medicine and to ensure the trigger fingers are completely pushed to the side. If the plunger is not fully depressed the needle shield will not extend to cover the needle when it is removed. If the needle is not covered, carefully place the syringe into the puncture resistant container to avoid injury with the needle.

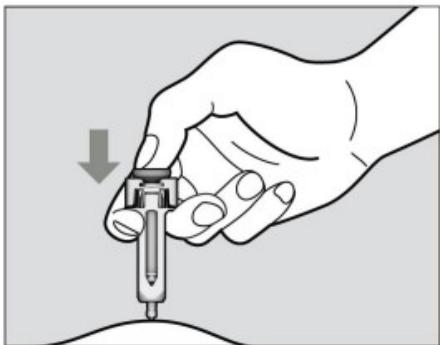


Figure H

- After the plunger is pushed all the way down, keep pressing down on the plunger to be sure all of the medicine is injected before taking the needle out of the skin.
- Keep pressing down on the plunger while you take the needle out of the skin at the same angle as inserted (See **Figure I**).

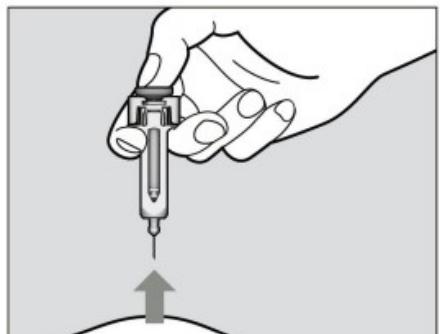


Figure I

- After the needle is removed completely from the skin, release the plunger, allowing the needle-shield to protect the needle (See **Figure J**).

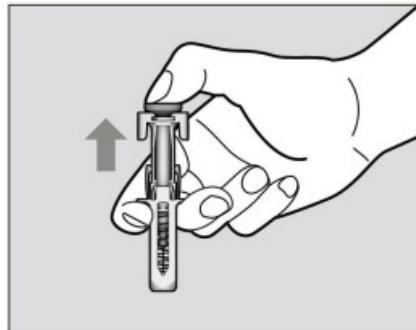


Figure J

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- Do not rub the injection site.
- If needed, you may cover the injection site with a small bandage.

Step 4. Dispose of the syringe

- The ACTEMRA prefilled syringe should not be reused.
- Put the used syringe into your puncture resistant container (See "How do I throw away used syringes?")
- Do not put the needle cap back on the needle.
- If your injection is given by another person, this person must also be careful when removing the syringe and disposing of the syringe to prevent accidental needle stick injury and passing infection.

How do I throw away used syringes?

- Put your used needles and syringes including ACTEMRA in a sharps disposal container right away after use (See **Figure K**). Do not throw away (dispose of) loose needles and syringes in your household trash.

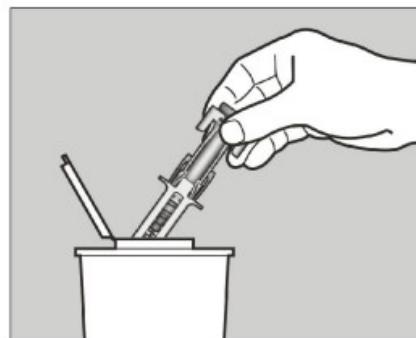


Figure K

- If you do not have a sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
 - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used needles and syringes.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- Keep ACTEMRA prefilled syringes and the disposal container out of the reach of children.

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any question or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ACTEMRA prefilled syringe, please contact your healthcare provider familiar with ACTEMRA.