SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Avtozma 162 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 162 mg of tocilizumab in 0.9 mL.

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against soluble and membrane-bound interleukin 6 receptors.

Excipients with known effect:
Polysorbate
Each 162 mg pre-filled syringe contains 0.2 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear to slightly opalescent, colourless to yellow solution with pH of 5.7 – 6.3 and an osmolality of 280 – 340 mmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Avtozma, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.
Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; 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. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

4.2 Posology and method of administration

Tocilizumab SC formulation is administered with a single-use pre-filled syringe with needle safety device. Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA and/or GCA. The pre-filled pen should not be used to treat paediatric patients < 12 years of age since there is a potential risk of intramuscular injection due to thinner subcutaneous tissue layer.

The first injection should be performed under the supervision of a qualified health care professional. A patient or parent/guardian can self-inject Avtozma only if the physician determines that it is appropriate and the patient or parent/guardian agrees to medical follow-up as necessary and has been trained in proper injection technique.

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.

All patients treated with Avtozma should be given the Patient Alert Card.

Suitability of the patient or parent/guardian for subcutaneous home use should be assessed and patients or parent/guardian instructed to inform a healthcare professional before administering the next dose if they experience symptoms of an allergic

reaction. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

Posology

RA
The recommended posology is subcutaneous 162 mg once every week.

Limited information is available regarding switching patients from Avtozma intravenous formulation to Avtozma subcutaneous fixed dose formulation. The once every week dosing interval should be followed.

Patients transitioning from intravenous to subcutaneous formulation should administer their first subcutaneous dose instead of the next scheduled intravenous dose under the supervision of a qualified healthcare professional.

GCA
The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. Avtozma can be used alone following discontinuation of glucocorticoids.
Avtozma monotherapy should not be used for the treatment of acute relapses (see 4.4).

Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

RA and GCA
Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

Laboratory Value	**Action**
> 1 to 3 x Upper Limit of Normal (ULN)	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate. For persistent increases in this range, reduce Avtozma dose frequency to every other week injection or interrupt Avtozma until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised. Restart with weekly or every other week injection, as clinically appropriate.
> 3 to 5 x ULN	Interrupt Avtozma dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN. For persistent increases > 3 x ULN (confirmed by repeat testing, see 4.4.), discontinue Avtozma.
> 5 x ULN	Discontinue Avtozma.

- 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 x 10^9/L

Laboratory Value (cells x 10^9/ L)	**Action**
ANC > 1	Maintain dose.
ANC 0.5 to 1	Interrupt Avtozma dosing. When ANC increases > 1 x 10^9/ L resume Avtozma dosing every other week and increase to every week injection, as clinically appropriate.
ANC < 0.5	Discontinue Avtozma.

- Low platelet count

Laboratory Value (cells x 10^3/ µL)	**Action**
50 to 100	Interrupt Avtozma dosing. When platelet count > 100 x 10^3/ µL resume Avtozma dosing every other week and increase to every week injection as clinically appropriate.
< 50	Discontinue Avtozma.

RA and GCA

Missed dose

If a patient misses a subcutaneous weekly injection of Avtozma within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a subcutaneous once every other week injection of Avtozma within 7 days of the scheduled dose, he/she should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

Special populations

Elderly:

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. Avtozma has not been studied in patients with severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients.

Hepatic impairment:

Avtozma has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

Paediatric patients

The safety and efficacy of Avtozma subcutaneous formulation in children from birth to less than 1 year have not been established. No data are available.

A change in dose should only be based on a consistent change in the patient's body weight over time.
Avtozma can be used alone or in combination with MTX.

sJIA Patients
The recommended posology in patients above 1 year of age is subcutaneous 162 mg once every week in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 2 weeks in patients weighing less than 30 kg.
Patients must have a minimum body weight of 10 kg when receiving Avtozma subcutaneously.

pJIA Patients:
The recommended posology in patients above 2 years of age is subcutaneous 162 mg once every 2 weeks in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 3 weeks in patients weighing less than 30 kg.

Dose adjustments due to laboratory abnormalities (sJIA and pJIA)

If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA or pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	**Action**
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt Avtozma until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt Avtozma dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue Avtozma. The decision to discontinue Avtozma in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/ L)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Avtozma dosing When ANC increases to > 1 x 10^9/ L resume Avtozma
ANC < 0.5	Discontinue Avtozma The decision to discontinue Avtozma in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10^3/ μL)	**Action**
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt Avtozma dosing When platelet count is > 100 x 10^3/ μL resume Avtozma
< 50	Discontinue Avtozma. The decision to discontinue Avtozma in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dosing frequency due to laboratory abnormalities has not been studied in sJIA or pJIA patients.

The safety and efficacy of Avtozma subcutaneous formulation in children with conditions other than sJIA or pJIA have not been established.

Available data with the IV formulation suggest that clinical improvement is observed within 12 weeks of initiation of treatment with tocilizumab. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

Missed dose

If a sJIA patient misses a subcutaneous weekly injection of Avtozma within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a subcutaneous once every 2 week injection of Avtozma within 7 days of the scheduled dose, he/she should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

If a pJIA patient misses a subcutaneous injection of Avtozma within 7 days of the scheduled dose, he/she should take the missed dose as soon as they remember and

take the next dose at the regular scheduled time. If a patient misses a subcutaneous injection of Avtozma by more than 7 days of the scheduled dose or is unsure when to inject Avtozma, call the doctor or pharmacist.

Method of administration
Avtozma is for subcutaneous use.
After proper training in injection technique, patients may self-inject with Avtozma if their physician determines that it is appropriate. The total content (0.9 mL) of the pre-filled syringe should be administered as a subcutaneous injection. 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.

The pre-filled syringe should not be shaken.

Comprehensive instructions for the administration of Avtozma in a pre-filled syringe are given in the package leaflet, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active, severe infections (see section 4.4).

6.4 Special warnings and precautions for use

Avtozma subcutaneous formulation is not intended for intravenous administration.

Avtozma subcutaneous formulation is not intended to be given to children with sJIA weighing less than 10 kg.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab (see section 4.8, Undesirable effects). Avtozma treatment must not be initiated in patients with active infections (see section 4.3). Administration of tocilizumab should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of Avtozma in patients with a history of recurring or chronic infections or with underlying conditions (e.g.) diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as Avtozma as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis
As recommended for other biological treatments, all patients should be screened for latent tuberculosis (TB) infection prior to starting Avtozma therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating Avtozma. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients and parents/guardians of sJIA or pJIA patients should be advised to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade (fever) suggestive of a tuberculosis infection occur during or after therapy with Avtozma.

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

Complications of diverticulitis
Events of diverticular perforations as complications of diverticulitis have been reported uncommonly in patients treated with tocilizumab (see section 4.8). Avtozma 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, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

Hypersensitivity reactions
Serious hypersensitivity reactions, including anaphylaxis have been reported in association with tocilizumab (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous treatment with Avtozma even if they have received premedication with steroids and antihistamines. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Avtozma should be stopped immediately, appropriate therapy initiated and tocilizumab should be permanently discontinued.

Active hepatic disease and hepatic impairment
Treatment with tocilizumab, particularly when administered concomitantly with MTX, 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 4.2 and 4.8).

Hepatotoxicity
Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with tocilizumab treatment (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with Avtozma. When clinically indicated, other liver function tests including bilirubin should be considered.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (see section 4.8). 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. Patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

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

In RA, GCA, pJIA and sJIA patients, 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 modifications, including Avtozma discontinuation, based on transaminases levels see section 4.2. For ALT or AST elevations > 3–5 x ULN, Avtozma treatment should be interrupted.

Haematological abnormalities
Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with tocilizumab, initiation is not recommended in patients with an ANC below 2 x 10^9/L. Caution should be exercised when considering initiation of Avtozma treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/μL). In patients who develop an ANC < 0.5 x 10^9/L or a platelet count < 50 x 10^3/μL, continued treatment is not recommended.

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with tocilizumab to date.

In RA and GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of the second administration and thereafter according to good clinical practice (see section 4.2).

Lipid parameters
Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with tocilizumab (see section 4.8). 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 all patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of Avtozma therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

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

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

Vaccinations
Live and live attenuated vaccines should not be given concurrently with Avtozma as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with Avtozma 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 immunisations in agreement with current immunisation guidelines prior to initiating Avtozma therapy. The interval between live vaccinations and initiation of Avtozma therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk
RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

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

GCA
Avtozma monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established. Glucocorticoids should be given according to medical judgement and practice guidelines.

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

<u>Excipients with known effect</u>

Polysorbate
Each 162 mg pre-filled syringe contains 0.2 mg of polysorbate 80.
Polysorbates may cause allergic reactions. Patients with polysorbate allergy should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on tocilizumab clearance in RA patients. In GCA patients, no effect of cumulative corticosteroid dose on tocilizumab exposure was observed.

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 Avtozma, 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 normalises expression of these enzymes.

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 to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy

There are no adequate data from the use of Avtozma in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown.

Avtozma should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether tocilizumab is excreted in human breast milk. The excretion of Avtozma in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Avtozma should be made taking into account the benefit of breast-feeding to the child and the benefit of Avtozma therapy to the woman.

Fertility

Available non-clinical data do not suggest an effect on fertility under Avtozma treatment.

4.7 Effects on ability to drive and use machines

Tocilizumab has a minor influence on the ability to drive and use machines (see section 4.8, dizziness).

4.8 Undesirable effects

Summary of the safety profile

The safety profile comes from 4510 patients exposed to tocilizumab in clinical trials; the majority of these patients were participating in adult RA studies (n=4009), while the remaining experience comes from GCA (n=149), pJIA (n=240) and sJIA (n=112) studies. The safety profile of tocilizumab across these indications remains similar and undifferentiated.

The most commonly reported Adverse Drug Reactions (ADRs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

Tabulated list of adverse reactions
ADRs from clinical trials and/or post marketing experience with tocilizumab based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and are presented by MedDRA system organ class. The corresponding frequency category for each AR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) rare, (1/10,000 to <1/1,000) or very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. List of ADRs occurring in patients treated with tocilizumab.

MedDRA System	Frequency categories with preferred terms

	Very Common	Common	Uncommon	Rare
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis	
Blood and lymphatic system disorders		Leukopenia, Neutropenia, Hypofibrinogenaemia		
Immune system disorders				Anaphylaxis (fatal)[1,2,3]
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia	
Nervous system disorders		Headache, Dizziness		
Eye disorders		Conjunctivitis		
Vascular disorders		Hypertension		
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea		
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer	
Hepatobiliary disorders				Drug-induced liver injury, Hepatitis, Jaundice, Very rare: Hepatic failure
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria		Stevens-Johnson-Syndrome[3]
Renal and urinary disorders			Nephrolithiasis	
General disorders and administration site conditions	Injection site reaction	Peripheral oedema Hypersensitivity reaction,		
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*		

* Includes elevations collected as part of routine laboratory monitoring (see text below)

[1] See section 4.3
[2] See section 4.4
[3] This adverse reaction was identified through post marketing surveillance but not observed in controlled 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.

Subcutaneous use

RA

The safety of subcutaneous tocilizumab in RA includes a double-blind, controlled, multicenter study, SC-I. SC-I was a non-inferiority study that compared the efficacy and safety of tocilizumab162 mg administered every week versus 8 mg/kg intravenous in 1262 patients with RA. All patients received background non-biologic DMARD(s). The safety and immunogenicity observed for tocilizumab administered subcutaneous was consistent with the known safety profile of intravenous tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions was observed in the subcutaneous arms compared with placebo subcutaneous injections in the intravenous arms.

Injection site reactions

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

Haematological abnormalities:

Neutrophils

During routine laboratory monitoring in the tocilizumab 6 month controlled clinical trial SC-I, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% of patients on the subcutaneous weekly dose.

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

Platelets

During routine laboratory monitoring in the tocilizumab 6 month clinical trial SC-I, none of the patients on the SC weekly dose had a decrease in platelet count to $\leq 50 \times 10^3/\mu L$.

Hepatic transaminase elevations

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

Lipid parameters

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

Subcutaneous Use

sJIA

The safety profile of subcutaneous tocilizumab was evaluated in 51 paediatric patients (1 to 17 years of age) with sJIA. 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
The rate of infection in sJIA patients treated with SC tocilizumab was comparable to sJIA patients treated with IV tocilizumab.

Injection Site Reactions (ISRs)
In the SC Study (WA28118), a total of 41.2% (21/51) sJIA patients experienced ISRs to tocilizumab SC. 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 required patient withdrawal from treatment or dose interruption.

Laboratory Abnormalities
In the 52-week open-label SC Study (WA28118), neutrophil count decrease to below 1 × 109/L occurred in 23.5% of patients treated with tocilizumab SC. Decreases in platelet counts to below $100 \times 10^3/\mu L$ occurred in 2% of the patients treated with tocilizumab SC. An elevation in ALT or AST to ≥3 x ULN occurred in 9.8% and 4.0% patients treated with tocilizumab SC, respectively.

Lipid parameters
In the 52-week open-label SC 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 at any time during study treatment, respectively.

Subcutaneous use

pJIA

The safety profile of subcutaneous tocilizumab was also evaluated in 52 paediatric patients with pJIA. The total patient exposure to tocilizumab in the pJIA all exposure population was 184.4 patient years for IV 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 pJIA patients experienced ISRs following SC tocilizumab injections compared to adult RA.

Infections
In the SC tocilizumab study, the rate of infection in pJIA patients treated with SC tocilizumab was comparable with pJIA patients treated with IV tocilizumab.

Injection Site Reactions
A total of 28.8% (15/52) pJIA patients experienced ISRs to tocilizumab SC. These ISRs occurred in a 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.

Laboratory Abnormalities
During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below $1 \times 10^9/L$ occurred in 15.4% of patients treated with SC tocilizumab. An elevation in ALT or AST ≥3 x ULN occurred in 9.6% and 3.8% patients treated with tocilizumab SC, respectively. No patients treated with SC tocilizumab experienced a decrease in platelet count to $\leq 50 \times 10^3/\mu L$.

Lipid parameters

In the SC Study, 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.

Subcutaneous Use

GCA
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).

Infections
The rate of infection/serious infection events was balanced between the tocilizumab weekly group (200.2/9.7 events per 100 patient years) vs. 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.

Injection site reactions
In the tocilizumab subcutaneous weekly group, a total of 6% (6/100) patients reported an adverse reaction occurring at the site of a subcutaneous injection. No injection site reaction was reported as a serious adverse event or required treatment discontinuation.

Haematological abnormalities:
Neutrophils
During routine laboratory monitoring in the tocilizumab 12 month controlled clinical trial, a decrease in neutrophil count below 1×10^9/L occurred in 4% of patients in the tocilizumab subcutaneous weekly group. This was not observed in either of the placebo plus prednisone taper groups.

Platelets
During routine laboratory monitoring in the tocilizumab 12 month controlled clinical trial, one patient (1%, 1/100) in the tocilizumab subcutaneous weekly group had a single transient occurrence of decrease in platelet count to $<100 \times 10^3/\mu$L without associated bleeding events. A decrease in platelet count below $100 \times 10^3/\mu$L was not observed in either of the placebo plus prednisone taper groups.

Hepatic transaminase elevations
During routine laboratory monitoring in the tocilizumab12 month controlled clinical trial, elevation in ALT ≥3 x ULN occurred in 3% of patients in the tocilizumab subcutaneous weekly group compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 week prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the tocilizumab subcutaneous weekly group, compared to no patients in either of the placebo plus prednisone taper groups.

Lipid parameters
During routine laboratory monitoring in the tocilizumab 12 month controlled clinical trial, 34% of patients experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the tocilizumab subcutaneous weekly group.

Intravenous use

RA

The safety of tocilizumab has been studied in 4 placebo-controlled studies (studies II, III, IV and V), 1 MTX-controlled study (study I) and their extension periods (see section 5.1).

The double-blind controlled period was 6 months in four studies (studies I, III, IV and V) and was up to 2 years in one study (study II). 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 or other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The long-term 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 the 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.

Description of selected adverse reactions

Infections

In the 6-month controlled studies the rate of all infections reported with tocilizumab 8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD group. In the long-term exposure population, the overall rate of infections with tocilizumab was 108 events per 100 patient years exposure.

In 6-month controlled clinical studies, the rate of serious infections with tocililzumab 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group.

In the long-term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

Interstitial lung disease

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

Gastrointestinal perforation

During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including

generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Infusion Related 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 plus DMARD group and 5.1% of patients in the placebo plus 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 anaphylactic reactions (occurring in a total of 8/4,009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous tocilizumab (see section 4.4).

Haematological abnormalities:
Neutrophils
In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/ L occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/ L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ L were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs. Infections with neutropenia have been reported.

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

Platelets
In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/μL occurred in 1.7% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events.

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

Very rare reports of pancytopenia have occurred in the post marketing setting.

Hepatic transaminase elevations

During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN 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 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 2 x ULN.

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

Lipid parameters
During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving tocilizumab in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ L, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ L. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

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

Malignancies
The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.

Skin Reactions
Rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

Immunogenicity
Anti-tocilizumab antibodies may develop during tocilizumab treatment. Correlation of antibody development to clinical response or adverse events may be observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play** or **Apple App Store**. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

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

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07.

Avtozma is a biosimilar medicinal product. Detailed information is available on the MHRA website.

Mechanism of action
Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

Pharmacodynamic effects
In RA clinical studies with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with tocilizumabwas associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In tocilizumab-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In GCA clinical 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 intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to their lowest 2 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. RA and GCA patients demonstrate a comparable (to healthy subjects) decrease of absolute neutrophil counts following tocilizumab administration (see section 4.8).

Subcutaneous use

RA

Clinical efficacy

The efficacy of subcutaneous administered tocilizumab in alleviating the signs and symptoms of RA and radiographic response, was assessed in two randomised, double-blind, controlled, multi-center studies. For study I (SC-I), patients were required to be >18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline. All patients received background non-biologic DMARD(s). For study II (SC-II), patients were required to be > 18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline.

Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.

Clinical response

Study SC-I evaluated patients with moderate to severe active RA 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. In SC-I, 1262 patients were randomized 1:1 to receive tocilizumab subcutaneous 162 mg every week or tocilizumab intravenous 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 2.

Table 2. ACR responses in study SC-I (% patients) at Week 24

	SC-I[a]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537
ACR20 Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50 Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70 Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	

TCZ = tocilizumab

a = Per Protocol Population

Patients in study SC-I had a mean Disease Activity Score (DAS28) at baseline of 6.6 and 6.7 on the subcutaneous and intravenous arms, respectively. At week 24, a significant reduction in DAS28 from baseline (mean improvement) of 3.5 was observed on both treatment arms, and a comparable proportion of patients had achieved DAS28 clinical remission (DAS28 < 2.6) on the subcutaneous (38.4%) and IV (36.9%) arms.

Radiographic response

The radiographic response of subcutaneous administered tocilizumab was assessed in a double-blind, controlled, multicenter study in patients with active RA (SC-II). Study SC-II evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. Patients were required to be >18 years of age with active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline. In SC-II, 656 patients were randomized 2:1 to tocilizumab subcutaneous 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 subcutaneous compared to placebo (mean 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.

In study SC-II, at week 24 there was ACR20 of 60.9%, ACR50 of 39.8% and ACR70 of 19.7% for patients treated with tocilizumab subcutaneous every other week versus placebo ACR20 of 31.5%, ACR50 of 12.3% and ACR70 of 5.0%. Patients had mean DAS28 at baseline of 6.7 on subcutaneous and 6.6 on placebo arms. At week 24, a significant reduction in DAS28 from baseline of 3.1 was observed on subcutaneous and 1.7 on placebo arm, and for DAS28 < 2.6, 32.0% was observed on subcutaneous and 4.0% on placebo arm.

Health-related and quality of life outcomes
In study SC-I, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 on both the subcutaneous and intravenous arms. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥0.3 units) was also comparable on the subcutaneous (65.2%) versus intravenous (67.4%) arms, with a weighted difference in proportions of - 2.3% (95% CI - 8.1, 3.4). For SF-36, the mean change from baseline at week 24 in the mental component score was 6.22 for the subcutaneous arm and 6.54 for the intravenous arm, and for the physical component score was also similar with 9.49 for the subcutaneous arm and 9.65 for the intravenous arm.

In study SC-II, mean decrease in HAQ-DI from baseline to week 24 was significantly greater for patients treated with tocilizumab subcutaneous every other week (0.4) versus placebo (0.3). Proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was higher for tocilizumab subcutaneous every other week (58%) versus placebo (46.8%). SF-36 (mean change in mental and physical component scores) was significantly greater with tocilizumab subcutaneous group (6.5 and 5.3) versus placebo (3.8 and 2.9).

Subcutaneous Use
sJIA
Clinical Efficacy
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 tocilizumab 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=26) dosed with 162 mg of tocilizumab every week (QW)

and patients weighing below 30 kg (n=25) dosed with 162 mg of tocilizumab every 10 days (Q10D; n=8) or every 2 weeks (Q2W; n=17) for 52 weeks. Of these 51 patients, 26 (51%) were naive to tocilizumab and 25 (49%) had been receiving tocilizumab IV and switched to tocilizumab SC at baseline.
Exploratory efficacy results showed that tocilizumab SC 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 tocilizumab IV to tocilizumab SC treatment over the entire course of the study for patients in both body weight groups (below 30 kg and ≥ 30 kg).

Subcutaneous Use

pJIA

Clinical Efficacy

A 52-week, open-label, multicenter, PK-PD and safety study was conducted in paediatric patients with pJIA, aged 1 to 17 years old, to determine the appropriate subcutaneous dose of tocilizumab 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 tocilizumab every 3 weeks (Q3W) for 52 weeks. Of these 52 patients, 37 (71%) were naive to tocilizumab and 15 (29%) had been receiving tocilizumab IV and switched to tocilizumab SC at baseline.

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

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

Subcutaneous Use

GCA

Clinical efficacy

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 Part 2 was 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 doses of tocilizumab (162 mg every week and 162 mg every other week) were compared to two different placebo control groups randomised 2:1:1:1.

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 duration of glucocorticoid therapy during screening and before tocilizumab (or placebo) was initiated, was similar in all 4 treatment groups (see Table 3).

Table 3. Duration of Corticosteroid Therapy During Screening in Study WA28119

	Placebo + 26 weeks prednisone taper	**Placebo + 52 weeks prednisone taper**	**tocilizumab 162mg SC weekly + 26 weeks prednisone taper**	**tocilizumab 162 mg SC every other weekly + 26 weeks prednisone taper**
	N=50	**N=51**	**N=100**	**N=49**
Duration (days)				
Mean (SD)	35.7 (11.5)	36.3 (12.5)	35.6 (13.2)	37.4 (14.4)
Median	42.0	41.0	41.0	42.0
Min - Max	6 - 63	12 – 82	1 - 87	9 - 87

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 4).

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 placebo plus 52 weeks prednisone taper, was also met (Table 4).

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 the Table 4.

Secondary Endpoints
The assessment of the time to first GCA flare showed a significantly lower risk of flare for the tocilizumab subcutaneous weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the

tocilizumab subcutaneous every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). tocilizumab subcutaneous 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 4).

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 4). 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 4. Efficacy results from Study WA28119

	Placebo + 26 weeks prednisone taper N=50	**Placebo + 52 weeks prednisone taper N=51**	**Tocilizumab 162mg SC weekly + 26 weeks prednisone taper N=100**	**Tocilizumab 162 mg SC every other weekly + 26 weeks prednisone taper N=49**
Primary Endpoint				
****Sustained remission (Tocilizumab groups vs Placebo+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 (Tocilizumab groups vs Placebo+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] (Tocilizumab groups vs Placebo+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] (Tocilizumab groups vs Placebo+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; Tocilizumab groups vs Placebo +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; Tocilizumab groups vs Placebo + 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; Tocilizumab groups vs Placebo +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; Tocilizumab groups vs Placebo + 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 (Tocilizumab groups vs Placebo+26[2])	3296.00	N/A	1862.00*	1862.00*
median at Week 52 (Tocilizumab groups vs Placebo +52[2])	N/A	3817.50	1862.00*	1862.00*
Exploratory Endpoints				

	Placebo + 26 weeks prednisone taper N=50	**Placebo + 52 weeks prednisone taper N=51**	**Tocilizumab 162mg SC weekly + 26 weeks prednisone taper N=100**	**Tocilizumab 162 mg SC every other weekly + 26 weeks prednisone taper N=49**
Annualized relapse rate, Week 52[§] Mean (SD)	1.74 (2.18)	1.30 (1.84)	0.41 (0.78)	0.67 (1.10)

* p<0.0001
** p<0.005 (threshold for significance for primary and key secondary tests of superiority)
***Descriptive p value <0.005
******Flare: recurrence of GCA signs or symptoms and/or ESR ≥30 mm/h** – Increase in the prednisone dose required
Remission: absence of flare and normalization of the CRP
Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper
[1] analysis of the time (in days) between clinical remission and first disease flare
[2] p-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

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 groups [placebo plus 26 weeks; -0.28, placebo 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: 8.6, 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 [weekly 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 [placebo plus 26 weeks -3.4, placebo plus 52 weeks -7.2], although only the tocilizumab every other weekly plus 26 weeks prednisone taper group showed a statistically significant difference compared to placebo [placebo plus 26 weeks taper p=0.0059, and placebo plus 52 weeks 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], placebo plus 26 weeks 0.26 [10.702], and placebo 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], placebo plus 26 weeks 0.07 [0.293], and placebo plus 52 weeks -0.02 [0.159]. Higher scores signal improvement in both FACIT-Fatigue and EQ5D.

Intravenous use

RA

Clinical efficacy

The efficacy of tocilizumab in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multi-centre studies. Studies I-V enrolled patients 18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline.

In Study I, tocilizumab was administered intravenously every four weeks as monotherapy. In Studies II, III and V, tocilizumab was administered intravenously every four weeks in combination with MTX vs. placebo and MTX. In Study IV, tocilizumab was administered intravenously every 4 weeks in combination with other DMARDs vs. placebo and other DMARDs. The primary endpoint for each of the five studies was the proportion of patients who achieved an ACR 20 response at week 24.

Study I evaluated 673 patients who had not been treated with MTX within six months prior to randomisation 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 mg to a maximum of 20 mg weekly over an eight week period).

Study II, a two year study with planned analyses at week 24, week 52 and week 104, 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 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with tocilizumab 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label tocilizumab 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 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 tocilizumab or placebo were given every four weeks, in combination with stable MTX (10 mg to 25 mg weekly).

Study IV evaluated 1,220 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 stable DMARDs.

Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomisation. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every four weeks in combination with stable MTX (10 mg to 25 mg weekly).

Clinical response

In all studies, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 5). In study I, superiority of tocilizumab 8 mg/kg was demonstrated against the active comparator MTX.

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 ongoing open label extension studies I-V.

In patients treated with tocilizumab 8 mg/kg, significant improvements were noted on all individual components of the ACR response including: tender and swollen joint counts; patients and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Patients in studies I – V had a mean Disease Activity Score (DAS28) of 6.5–6.8 at baseline. Significant reduction in DAS28 from baseline (mean improvement) of 3.1–3.4 were observed in tocilizumab-treated patients compared to control patients (1.3-2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 < 2.6) was significantly higher in patients receiving tocilizumab (28–34%) compared to 1–12% of control patients at 24 weeks. In study II, 65% of patients achieved a DAS28 <2.6 at week 104 compared to 48% at 52 weeks and 33% of patients at week 24.

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the tocilizumab 8 mg/kg plus DMARD vs. the tocilizumab 4 mg/kg plus DMARD group ($p< 0.03$). Similarly the proportion of patients achieving a DAS 28 remission (DAS28 < 2.6) was significantly higher (31% vs. 16% respectively) in patients receiving tocilizumab 8 mg/kg plus DMARD than in patients receiving tocilizumab 4 mg/kg plus DMARD ($p< 0.0001$).

Table 5. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% patients)

	Study I AMBITION		**Study II LITHE**		**Study III OPTION**		**Study IV TOWARD**		**Study V RADIATE**	
Week	**TCZ 8 mg/kg**	**MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + DMARD**	**PBO + DMARD**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**
	N = 286	**N = 284**	**N = 398**	**N = 393**	**N = 205**	**N = 204**	**N = 803**	**N = 413**	**N = 170**	**N = 158**
ACR 20										
24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
52			56%***	25%						
ACR 50										
24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%

52			36%***	10%						
ACR 70										
24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
52			20%***	4%						

TCZ - Tocilizumab
MTX - Methotrexate
PBO - Placebo
DMARD - Disease modifying anti-rheumatic drug
** *- p< 0.01, TCZ vs. PBO + MTX/DMARD*
*** *- p< 0.0001, TCZ vs. PBO + MTX/DMARD*

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

Radiographic response
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 (Table 6).

In the open-label extension of Study II the inhibition of progression of structural joint damage in tocilizumab plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at week 104 in total Sharp-Genant score was significantly lower for patients randomised to tocilizumab 8 mg/kg plus MTX ($p<0.0001$) compared with patients who were randomised to placebo plus MTX.

Table 6. Radiographic mean changes over 52 weeks in Study II

	PBO + MTX (+ TCZ from week 24) N = 393	**TCZ 8 mg/kg + MTX N = 398**
Total Sharp-Genant score	1.13	0.29*
Erosion score	0.71	0.17*
JSN score	0.42	0.12**

PBO - Placebo
MTX - Methotrexate
TCZ - Tocilizumab
JSN - Joint space narrowing
* *- p≤ 0.0001, TCZ vs. PBO + MTX*
** *- p< 0.005, TCZ vs. PBO + MTX*

Following 1 year of treatment with tocilizumab plus MTX, 85% of patients(n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo plus MTX-treated patients(n=290) (p □ 0.001). This remained consistent following 2 years of treatment (83%; n=353). Ninety three percent (93%; n=271) of patients had no progression between week 52 and week 104.

Health-related and quality of life outcomes

tocilizumab-treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with tocilizumab compared with patients treated with DMARDs. During the open-label period of Study II, the improvement in physical function has been maintained for up to 2 years. At Week 52, the mean change in HAQ-DI was -0.58 in the tocilizumab 8 mg/kg plus MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the tocilizumab 8 mg/kg plus MTX group (-0.61).

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with tocilizumab compared with DMARDs ($p< 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy
Study VI (WA19924), a 24 week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, 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 7).

Table 7: Efficacy Results for Study VI (WA19924)

	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 (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

[a] *p value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.*

[b] *Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure*

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%). The types of adverse drug reactions in the tocilizumab arm were consistent with the known

safety profile of tocilizumab and adverse drug reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the tocilizumab arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). 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).

5.2 Pharmacokinetic properties

The pharmacokinetics 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.

RA

Intravenous use

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg tocilizumab every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h μg/mL, trough concentration (C_{min}) = 15.9 ± 13.1 μg/mL and maximum concentration (C_{max}) = 182 ± 50.4 μg/mL, and. the accumulation ratios for AUC and C_{max} were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for C_{min} (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{max} and after 8 and 20 weeks for AUC and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 50000 ± 16800 μg•h/mL, 24.4 ± 17.5 μg/mL, and 226 ± 50.3 μg/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each

incremental increase in tocilizumab concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution

In RA patients the central volume of distribution was 3.72, the peripheral volume of distribution was 3.35 resulting in a volume of distribution at steady state of 7.07.

Elimination

Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 9.5 mL/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

Linearity

Pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in the AUC and C_{min} was observed for doses of 4 and 8 mg/kg every 4 weeks. C_{max} increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 3.2 and 30 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Subcutaneous use

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with 162 mg subcutaneous every week, 162 mg subcutaneous every other week, and or 4 or 8 mg/kg intravenous every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. For the 162 mg every week dose, the predicted mean (±SD) steady-state AUC1week, C_{min} and C_{max} of tocilizumab were 7970 ± 3432 µg•h/mL, 43.0 ± 19.8 µg/mL, and 49.8 ± 21.0 µg /mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.32, 6.30, and 5.27, respectively. Steady state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the 162 every other week dose, the predicted mean (±SD) steady-state AUC2week, C_{min}, and C_{max} of tocilizumab were 3430 ± 2660 µg•h/mL, 5.7 ± 6.8 µg/mL, and 13.2 ± 8.8 µg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 6.02, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

Absorption

Following subcutaneous dosing in RA patients, the time to peak serum tocilizumab concentrations tmax was 2.8 days. The bioavailability for the subcutaneous formulation was 79%.

Elimination
For subcutaneous administration, the concentration-dependent apparent t 1/2 is up to 12 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

sJIA
Subcutaneous Use
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).

Limited data are available regarding exposures following subcutaneous administration of tocilizumab in sJIA patients below 2 years of age with a body weight less than 10 kg.

Patients with sJIA must have a minimum body weight of 10 kg when receiving tocilizumab subcutaneously (see section 4.2).

Table 8. Predicted mean ± SD PK parameters at steady-state after SC dosing in sJIA

Tocilizumab PK Parameter	**162 mg QW ≥ 30 kg**	**162 mg Q2W below 30 kg**
C_{max} (µg/mL)	99.8 ± 46.2	134 ± 58.6
C_{min} (µg/mL)	79.2 ± 35.6	65.9 ± 31.3
C_{mean} (µg/mL)	91.3 ± 40.4	101 ± 43.2
Accumulation C_{max}	3.66	1.88
Accumulation C_{min}	4.39	3.21
Accumulation C_{mean} or AUC_{τ}*	4.28	2.27

*τ = 1 week or 2 weeks for the two SC regimens

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

Absorption
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%.

Distribution
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

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 5.7 mL/h in paediatric patients with systemic juvenile idiopathic arthritis. 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.

pJIA

Subcutaneous use

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 9. Predicted mean ± SD PK parameters at steady-state after SC dosing in pJIA

Tocilizumab PK Parameter	**162 mg Q2W ≥ 30 kg**	**162 mg Q3W below 30 kg**
C_{max} (µg/mL)	29.4 ± 13.5	75.5 ± 24.1
C_{min} (µg/mL)	11.8 ± 7.08	18.4 ± 12.9
C_{avg} (µg/mL)	21.7 ± 10.4	45.5 ± 19.8
Accumulation C_{max}	1.72	1.32
Accumulation C_{min}	3.58	2.08
Accumulation C_{mean} or AUC_{τ} *	2.04	1.46

*τ = 2 week or 3 week for the two SC regimens

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.

Absorption

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%.

Distribution

In paediatric patients with pJIA, the central volume of distribution was 1.97 L, the peripheral volume of distribution was 2.03 L, resulting in a volume of distribution at steady state of 4.0 L.

Elimination

Population pharmacokinetic analysis for pJIA patients showed body size related impact on linear clearance so that body-weight based dosing should be taken into consideration (see Table 9).

After subcutaneous administration, the effective t1/2 of tocilizumab in pJIA patients is up to 10 days for patients < 30 kg (162 mg SC Q3W) and up to 7 days for patients >= 30 kg (162 mg SC Q2W) during a dosing interval at steady state. Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 6.25 mL/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

GCA

Subcutaneous use

The PK of tocilizumab in GCA patients were determined using a population PK model from an analysis dataset composed of 149 GCA patients treated with 162 mg subcutaneous every week or 162 mg subcutaneous every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients (see Table 10).

Table 10. Predicted mean ± SD PK parameters at steady-state after subcutaneous dosing in GCA

	Subcutaneous	
Tocilizumab PK Parameter	**162 mg every other weekly**	**162 mg weekly**
C_{max} (µg/mL)	19.3 ± 12.8	73 ± 30.4
C_{trough} (µg/mL)	11.1 ± 10.3	68.1± 29.5
C_{mean} (µg/mL)	16.2 ± 11.8	71.3 ± 30.1
Accumulation C_{max}	2.18	8.88
Accumulation C_{trough}	5.61	9.59
Accumulation C_{mean} or AUC_{τ} *	2.81	10.91

*τ = 2 week or 1 week for the two SC regimens

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 weekly dose. Approximately 90% of the steady-state (AUC) was reached by week 14 in the every other weekly and week 17 in the weekly dose groups.

Based on the current characterization of PK, tocilizumab trough concentration at steady state are 50% higher in this population relative to average concentrations in a large dataset from the RA population. These differences occur due to unknown reasons. PK differences are not accompanied by marked differences in PD parameters and so the clinical relevance is unknown.

In GCA patients, higher exposure was observed in patients with lower body weight. For the 162 mg every week dosing regimen, the steady-state Cavg was 51% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. For the 162 mg every other week regimen, the steady-state Cavg was 129% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg (n=7).

Absorption

Following subcutaneous dosing in GCA patients, the absorption t½ was around 4 days. The bioavailability for the SC formulation was 0.8. The median values of Tmax were 3 days after the tocilizumab weekly dose and 4.5 days after the tocilizumab every other week dose.

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 steady state of 7.46 L.

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 6.7 mL/h in GCA patients,

In GCA patients, at steady state, the effective t ½ 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 ½ of approximately 32 days was derived from the population parameter estimates.

Special populations
Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been 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 GCA study 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.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in RA and GCA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

Results of the population PK analysis for sJIA and pJIA patients confirmed that body size is the only covariate which has an appreciable impact on the pharmacokinetics of tocilizumab including elimination and absorption so that body-weight based dosing should be taken into consideration (see Tables 8 and 9).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential.

Available non-clinical data demonstrated the effect of IL-6 on malignant progression and apoptosis resistance to various cancer types. This data does not suggest a relevant risk for cancer initiation and progression under tocilizumab treatment. Additionally, proliferative lesions were not observed in a 6-month chronic toxicity study in cynomolgus monkeys or in IL-6 deficient mice.

Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment. Effects on endocrine active and reproductive system organs were not observed in a chronic cynomolgus monkey toxicity study and reproductive performance was not affected in IL-6 deficient mice. tocilizumab administered to cynomolgus monkeys during early gestation, was observed to have no direct or indirect harmful effect on pregnancy or embryonal-foetal development. However, a slight increase in abortion/embryonal-foetal death was observed with high systemic exposure (> 100 x human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to tocilizumab cannot be excluded.

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 intravenous and subcutaneous routes of administration.

6.5 List of excipients

L-Histidine
L-Histidine monohydrochloride monohydrate
L-Threonine
L-Methionine
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.6 Shelf life

42 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Once removed from the refrigerator, the pre-filled pen can be stored up to 3 weeks at or below 30°C.

Keep the pre-filled pen in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

0.9 mL solution in a pre-filled syringe (type I glass) with a staked-in needle containing 162 mg Avtozma assembled into a pre-filled pen. The syringe is closed by a rigid needle shield (polyisoprene rubber and polypropylene) and a sterile fluorotec-coated elastomeric plunger stopper (with silicone).

The Avtozma pre-filled pen for patient use is available in packs containing:

- 1 pre-filled pen
- 4 pre-filled pens
- 12 (3 packs of 4) pre-filled pens (Multipacks)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Avtozma is supplied in a single use pre-filled pen. After removing the pre-filled pen from the refrigerator the pre-filled pen should be allowed to reach room temperature (18°C to 28°C) by waiting for 45 minutes, before injecting Avtozma. The pen should not be shaken. After removing the cap the injection must be started within 3 minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled pen is not used within 3 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled pen.

If following pressing the needle cover the orange indicator does not move, you must dispose of the pre-filled pen in a puncture resistant container. Do not try to re-use the pre-filled pen. The pre-filled pen is locked and the needle is covered inside the needle cover when trying to re-use. Do not repeat the injection with another pre-filled pen. Call your healthcare provider for help.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to yellow, or any part of the pre-filled pen appears to be damaged.

Comprehensive instructions for the administration of Avtozma in a pre-filled pen are given in the package leaflet.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Celltrion Healthcare United Kingdom Limited
The Charter Building, Charter Place,
Uxbridge UB8 1JG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 51808/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/04/2025

10 DATE OF REVISION OF THE TEXT

19/11/2025