Actemra®

Tocilizumab

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Tocilizumab is a recombinant humanized anti-human interleukin6 (IL6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass.

ATC Code: L04AC07.

1.2 Type of Dosage Form

Intravenous (IV) formulation: Concentrate solution for infusion.

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

1.3 Route of Administration

Intravenous (IV) infusion.

Subcutaneous (SC) injection.

1.4 Sterile / Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

Active ingredient: tocilizumab.

Tocilizumab solution for intravenous (IV) infusion is a clear to opalescent, colourless to pale yellow liquid, supplied in preservative-free, non-pyrogenic single-use vials, supplied in 10 ml and 20 ml vials containing 4 ml, 10 ml or 20 ml of tocilizumab (20 mg/ml).

Excipients: polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections.

Tocilizumab solution for subcutaneous (SC) injection is a yellowish, preservative-free liquid supplied in a ready-to-use, single-use pre-filled syringe with needle safety device (PFS+NSD) or single-use pre-filled pen. Each device delivers 0.9 ml (162 mg) of tocilizumab.

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

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Rheumatoid Arthritis (RA) [IV and SC formulations]

Tocilizumab is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. Tocilizumab can be used alone or in combination with methotrexate (MTX) and/or other disease-modifying anti-rheumatic drugs (DMARDs). Tocilizumab has been shown to inhibit progression of joint damage as measured by X-ray and to improve physical function.

Giant Cell Arteritis (GCA) [SC formulation only]

Tocilizumab is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

Coronavirus disease 2019 (COVID-19) [IV formulation only]

Tocilizumab is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV and SC formulations]

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

Systemic Juvenile Idiopathic Arthritis (sJIA)

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

Subcutaneous Formulation

Tocilizumab is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 1 year of age and older.

Tocilizumab IV and SC can be given alone or in combination with MTX.

2.2 Dosage and Administration

General

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

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

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

For adult patients with COVID-19, tocilizumab is administered as an IV infusion

For patients with pJIA, tocilizumab is administered as an IV infusion or a SC injection.

For patients with sJIA, tocilizumab is administered as an IV infusion or a SC injection.

Intravenous Administration

Tocilizumab IV formulation is not intended for subcutaneous administration.

Tocilizumab IV formulation should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (see section 4.2 Special Instructions for Use, Handling and Disposal). The recommended duration of IV infusion is 1 hour.

Subcutaneous Administration

Tocilizumab SC formulation is not intended for intravenous administration.

Tocilizumab SC formulation is administered with a single-use PFS+NSD or pre-filled pen. The first injection should be performed under the supervision of a qualified health care professional. A patient can self-inject Actemra only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and has been trained in proper injection technique. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

Patients who transition from tocilizumab IV therapy to SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified health care professional.

Assess suitability of patient or parent/guardian for SC home administration and instruct the patient or parent/guardian to inform a healthcare professional before administering the next dose, if any symptoms of allergic reaction are experienced. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (see section 2.4.1 Warnings and Precautions, General and 2.6 Undesirable Effects).

Rheumatoid Arthritis [IV and SC formulations]

Intravenous Dosing Regimen

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

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

Subcutaneous Dosing Regimen

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

Giant Cell Arteritis (GCA) [SC formulation only]

The recommended dose of tocilizumab for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids. Tocilizumab can be used alone following discontinuation of glucocorticoids.

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

Dose Modification Recommendations for RA and GCA:

(See section 2.4.1 Warnings and Precautions, General)

- Liver enzyme abnormalities

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate For patients on intravenous tocilizumab (RA only) with persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until ALT/AST have normalized. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate. For patients on subcutaneous tocilizumab with persistent increases in this range, reduce tocilizumab injection frequency to every other week or interrupt tocilizumab until ALT/AST have normalized. Restart with weekly injection or injection every other week, as clinically appropriate.
> 3 to 5x ULN	Interrupt tocilizumab dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN (confirmed by repeat testing, see section 2.4.1), discontinue tocilizumab
> 5x ULN	Discontinue tocilizumab

- Low absolute neutrophil count (ANC)

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

- Low platelet count

Lab Value (cells x 10^3/µl)	Action
50 to 100	Interrupt tocilizumab dosing For patients on intravenous tocilizumab (RA only), when platelet count is > 100 x 10^3/µl resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. For patients on subcutaneous tocilizumab, when platelet count is > 100 x 103/µl resume tocilizumab injection every other week and increase frequency to every week, as clinically appropriate
< 50	Discontinue tocilizumab

COVID-19 [IV formulation only]

The recommended dose of tocilizumab for treatment of adult patients with COVID-19 is a single 60-minute infusion of 8 mg/kg

If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab 8 mg/kg may be administered at least 8 hours after the initial infusion

Doses exceeding 800 mg per infusion are not recommended in patients with COVID-19.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV and SC formulations]

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

Intravenous Dosing Regimen:

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

- 10 mg/kg for patients below 30 kg,
- 8 mg/kg for patients ≥ 30 kg,

given once every four weeks as an IV infusion.

Subcutaneous Dosing Regimen:

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

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

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

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

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

Intravenous Dosing Regimen:

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

- 12 mg/kg for patients below 30 kg,
- 8 mg/kg for patients ≥ 30 kg,

given once every two weeks as an IV infusion.

Subcutaneous Dosing Regimen:

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

- 162 mg once every two weeks for patients below 30 kg,
- 162 mg once every week for patients ≥ 30 kg
- Patients between 1 year and 2 years of age must have a minimum body weight of 10 kg when receiving 162 mg SC tocilizumab.

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

Dose Modification Recommendations for pJIA and sJIA:

Dose reduction of tocilizumab has not been studied in the pJIA or sJIA population. Dose interruptions of tocilizumab for laboratory abnormalities are recommended in patients with pJIA or sJIA and are similar to what is outlined above for patients with RA and GCA (also see section 2.4.1 Warnings and Precautions, General). If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. In pJIA or sJIA the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

2.2.1 Special Dosage Instructions

Pediatric use:

The safety and efficacy in patients aged less than 2 years in pJIA has not been established. The safety and efficacy in patients aged less than 2 years with IV TCZ in sJIA or less than 1 year with SC TCZ in sJIA have not been established.

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

Renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment (see section 3.2.4 Pharmacokinetics in Special Populations). Tocilizumab has not been studied in patients with severe renal impairment.

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

2.3 Contraindications

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

2.4 Warnings and Precautions

2.4.1 General

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

All Indications

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab (see section 2.6 Undesirable Effects). Tocilizumab treatment should not be initiated in patients with active infections. Administration of tocilizumab should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring infection or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections.

In patients with COVID-19, tocilizumab should not be administered if patients also have any other concurrent serious active infection .

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents, such as tocilizumab, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute-phase reactants. Patients (which include younger children who may be less able to communicate their symptoms) and parents/guardians of minors should be instructed to contact a healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Complications of Diverticulitis

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

Tuberculosis

As recommended for other biologic therapies, all patients should be screened for latent tuberculosis infection prior to starting tocilizumab therapy. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating tocilizumab.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with tocilizumab as clinical safety has not been established.

No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab.

In a randomised open-label study, adult RA patients treated with tocilizumab and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus-toxoid vaccines which was comparable to the response seen in patients on MTX only.

It is recommended that all patients, particularly pediatric or elderly patients, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating tocilizumab therapy. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Hypersensitivity Reactions

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

Active Hepatic Disease and Hepatic Impairment

Treatment with tocilizumab particularly when administered concomitantly with methotrexate, may be associated with elevations in hepatic transaminases, therefore caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 2.2.1 Special Dosage Instructions and 2.6.1 Undesirable Effects, Clinical Trials).

Hepatotoxicity

Mild and moderate elevations of hepatic transaminases have been observed with tocilizumab treatment (see section 2.6.1 Undesirable Effects, Clinical Trials). Increased frequency of these elevations was observed when drugs, which are known to cause hepatotoxicity (e.g. methotrexate (MTX)), were used in combination with tocilizumab.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (see section 2.6.2 Undesirable Effects, Post Marketing Experience). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of tocilizumab. Cases of liver failure resulting in liver transplantation have been reported.

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

In RA, GCA, pJIA and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended dose modifications, including tocilizumab discontinuation, based on transaminases, see section 2.2 Dosage and Administration.

Patients hospitalized with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19. The decision to administer tocilizumab should balance the potential benefit against the risks of acute treatment

with tocilizumab. In COVID-19 patients with elevated ALT or AST above 10 x ULN, administration of tocilizumab treatment is not recommended.

In COVID-19 patients, ALT/AST should be monitored according to current standard clinical practices

Viral Reactivation

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

Demyelinating Disorders

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

Neutropenia

Treatment with tocilizumab was associated with a higher incidence of neutropenia. Treatment-related neutropenia was not associated with serious infection in clinical trials (see section 2.6.1 Undesirable Effects, Clinical Trials).

Caution should be exercised when considering initiation of tocilizumab treatment in patients with a low neutrophil count i.e. absolute neutrophil count (ANC) below 2 x 10^9/L. In RA, GCA, pJIA and sJIA patients with an absolute neutrophil count below 0.5 x 10^9/L, treatment is not recommended [8]. In COVID-19 patients with an ANC below 1 x 10^9/L, administration of treatment is not recommended

In RA and GCA Patients, the neutrophils count should be monitored 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on ANC results, see section 2.2 Dosage and Administration.

In pJIA and sJIA patients, the neutrophils count should be monitored at the time of the second administration and thereafter according to good clinical practice (see section 2.2 Dosage and Administration, Dose modifications).

In COVID-19 patients, the neutrophil count should be monitored according to current standard clinical practices

Thrombocytopenia

Treatment with tocilizumab was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials (see section 2.6.1 Undesirable Effects, Clinical Trials).

Caution should be exercised when considering initiation of tocilizumab treatment in patients with a platelet count below 100 x $10^3/\mu$L. In all patients, including COVID-19, with a platelet count below 50 x $10^3/\mu$L treatment is not recommended.

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

In pJIA and sJIA Patients, platelets should be monitored at the time of the second administration and thereafter according to good clinical practice (see section 2.2 Dosage and Administration, Dose modifications).

In COVID-19 patients, platelets should be monitored according to current standard clinical practices

Lipids parameters

Elevations of lipid parameters such as total cholesterol, triglycerides and/or low density lipoprotein (LDL) cholesterol have been observed (see section 2.6.1 Undesirable Effects, Clinical Trials).

In patients treated with tocilizumab, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of tocilizumab therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Systemic Juvenile Idiopathic Arthritis

Macrophage Activation Syndrome (MAS)

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

2.4.2 Drug Abuse and Dependence

No studies on the effects on the potential for tocilizumab to cause dependence have been performed. However, there is no evidence from the available data that tocilizumab treatment results in dependence.

2.4.3 Ability to Drive and Use Machines

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

2.5 Use in Special Populations

2.5.1 Pregnancy

There are no adequate data from the use of tocilizumab in pregnant women. A study in monkeys did not indicate any dysmorphogenic potential but has yielded a higher number of spontaneous abortion / embryo-fetal death at a high dose (see section 3.3 Preclinical Safety, 3.3.5 Other). The relevance of these data for humans is unknown.

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

2.5.2 Labour and Delivery

No text

2.5.3 Nursing Mothers

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

2.5.4 Pediatric Use

(See section 2.2.1 Special Dosage Instructions.)

2.5.5 Geriatric Use

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

2.5.6 Renal Impairment

(See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.)

2.5.7 Hepatic Impairment

(See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.)

2.6 Undesirable Effects

2.6.1 Clinical Trials

The safety profile in this section comes from 5484 patients exposed to tocilizumab in clinical trials; the majority of these patients were participating in RA studies (n=4009), while the remaining experience comes from COVID-19 (n=974), pJIA (n=240), sJIA (n= 112), and GCA (n=149) studies. The safety profile of tocilizumab across these indications remains similar and undifferentiated.

Adverse Drug Reactions (ADRs) from clinical trials (Table 1) are listed by MedDRA system organ class according to clinical importance to the patient. The corresponding frequency category for each ADR is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10) or uncommon (≥1/1000 to < 1/100).

Table 1 Summary of ADRs occurring in RA, GCA, pJIA and sJIA **patients treated with tocilizumab**

MedDRA System Organ Class	**Very Common**	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infections	Cellulitis, Oral Herpes simplex, Herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, mouth ulceration, gastritis	Stomatitis, gastric ulcer
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria	
Nervous system disorders		Headache, dizziness	
Investigations		Hepatic transaminases increased, weight increased	Total bilirubin increased

Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leucopenia, neutropenia	
Metabolism and nutrition disorders		Hypercholesterolemia	Hypertriglyceridemia
General disorders and administration site conditions	Injection site reaction	Peripheral edema, hypersensitivity reaction,	
Respiratory, thoracic and mediastinal disorders		Cough, dyspnea	
Eye disorders		Conjunctivitis	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

Description of selected adverse drug reactions from clinical trials:

Rheumatoid Arthritis

Patients Treated with Intravenous Tocilizumab

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

The all-control population includes all patients from the double-blind phases of each core study from randomisation until either the first change in the treatment regimen, or two years is reached. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind controlled studies 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1870 patients received tocilizumab 8 mg/kg in combination with MTX/other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The all-exposure population includes all patients who received at least one dose of tocilizumab either in the double-blind control period or open-label extension phase in studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years.

Infections

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

In the 6-month controlled clinical trials the rate of serious infections (bacterial, viral and fungal) with tocilizumab 8 mg/kg+DMARD was 5.3 events per 100 pt years exposure compared to 3.9 events per 100 pt years exposure in the placebo+DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 pt years of exposure in the tocilizumab group and 1.5 events per 100 pt years of exposure in the MTX group.

In the all-exposure population the overall rate of serious infections was 4.7 events per 100 pt years. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, Herpes zoster, gastroenteritis, diverticulitis, sepsis, bacterial arthritis. Cases of opportunistic infections have also been reported.

Gastrointestinal Perforation

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

Infusion Reactions

In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 8 mg/kg+DMARD and 5.1% of patients in the placebo+DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment-limiting.

The rate of anaphylaxis (occurring in a total of 6/3778 patients) was several-fold higher in the 4 mg/kg arm in comparison to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with tocilizumab during the controlled and open-label clinical trials. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 2.4.1 Warnings and Precautions, General).

Immunogenicity

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

Early Rheumatoid Arthritis

Study VI (WA19926) evaluated 1162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the tocilizumab treatment groups was consistent with the known safety profile of tocilizumab (see Table 1) (see section 3.1.2 Clinical/Efficacy Studies).

Monotherapy: tocilizumab versus adalimumab

In a 24-week double-blinded, parallel study (monotherapy with tocilizumab 8 mg/kg IV q4w [N=162] compared to adalimumab 40 mg SC q2w [N=162]), the overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%) with the most common event being infections (3.1% each). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC

grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/l (25 mg/dl) for patients in the tocilizumab arm and 0.19 mmol/l (7 mg/dl) for patients in the adalimumab arm. The safety profile observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1) (see section 3.1.2 Clinical/Efficacy Studies).

Patients Treated with Subcutaneous Tocilizumab

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

Injection Site Reactions (ISRs)

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

Immunogenicity

In SC-I, a total of 625 patients treated with tocilizumab 162 mg weekly were tested for anti-tocilizumab antibodies in the 6 month controlled period. Five patients (0.8%) developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies.

A total of 1454 SC tocilizumab all exposure patients have been tested for anti-tocilizumab antibodies, thirteen patients (0.9%) developed positive anti-tocilizumab antibodies, and of these 12 patients (0.8%) developed neutralizing anti-tocilizumab antibodies.

No correlation of antibody development to clinical response or adverse events was observed.

Giant Cell Arteritis

The safety of subcutaneous tocilizumab has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the tocilizumab all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the tocilizumab treatment groups was consistent with the known safety profile of tocilizumab (see Table 1) (see section 3.1.2 Clinical/Efficacy Studies).

Infections

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

COVID-19

The safety evaluation of tocilizumab in COVID-19 was based on 3 randomized, double-blind, placebo controlled trials (studies ML42528, WA42380, and WA42511). A total of 974 patients were exposed to tocilizumab in these studies. Safety data from RECOVERY (Randomised Evaluation of COVID-19 Therapy) is not provided here as collection of adverse event data was limited.

The following adverse reactions, listed by MedDRA system organ class in Table 2, have been adjudicated from events which occurred in at least 3% of tocilizumab treated patients and more commonly than in patients on placebo in the pooled safety-evaluable population from clinical studies ML42528, WA42380, and WA42511.

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2: Summary of Adverse Reactions[1] Occurring in COVID-19 patients treated with tocilizumab[2] [113]

MedDRA System Organ Class	AE Term(s)	TCZ Incidence N=974 n (%)	Frequency
Hepatobilliary disorders	Hepatic transaminases increased	96 (9.9)	Common
Gastrointestinal disorders	Constipation	88 (9.0)	Common
	Diarrhoea	37 (3.8)	Common
	Nausea	33 (3.4)	Common
Infections and infestations	Urinary tract infection	49 (5.0)	Common
Vascular disorders	Hypertension	42 (4.3)	Common
Metabolism and nutrition disorders	Hypokalaemia	39 (4.0)	Common
Psychiatric disorders	Anxiety	38 (3.9)	Common
	Insomnia	36 (3.7)	Common

[1]Patients are counted once for each category regardless of the number of reactions
[2]Includes adjudicated reactions reported in studies WA42511, WA42380 and ML42528

Description of selected adverse drug reactions from clinical trials

Infections

In the pooled safety-evaluable population from the studies ML42528, WA42380, and WA42511, the rates of infection/serious infection events were balanced between COVID-19 patients receiving tocilizumab (30.3%/18.6%, n=974) versus placebo (32.1%/22.8%, n=483).

The safety profile observed in the subgroup of patients receiving baseline systemic corticosteroids (597 and 315 patients in the tocilizumab and placebo arms, respectively) was consistent with the safety profile in the overall safety-evaluable population presented in Table 2. In this subgroup, infections and serious infections occurred in 27.8% and 18.1% of patients treated with tocilizumab and in 30.5% and 22.9% of patients treated with placebo, respectively.

Polyarticular Juvenile Idiopathic Arthritis

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

Infections

Infections are the most commonly observed events in pJIA The rate of infections in the pJIA IV tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing below 30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing below 30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%). The rate of infection in pJIA patients treated with SC tocilizumab was comparable with pJIA patients treated with IV tocilizumab.

Infusion Reactions

In pJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion with IV tocilizumab. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion, and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients (see section 2.6 Undesirable Effects).

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

Injection Site Reactions

A total of 28.8% (15/52) pJIA patients experienced ISRs to SC tocilizumab. These ISRs occurred in 44% of patients >30 kg compared to 14.8% of patients below 30 kg. The most common ISRs

were injection site erythema, swelling, hematoma, pain and pruritis. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

Immunogenicity

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

Systemic Juvenile Idiopathic Arthritis

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

In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see section 2.6 Undesirable Effects above).

Infections

In the 12-week controlled trial the rate of all infections in the tocilizumab group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the ongoing open-label extension study (Part II) the overall rate of infections remained similar at 306.6 per 100 patient years.

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

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

Infusion Reactions

For sJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12-week controlled trial, four percent (4.0%) of patients from the tocilizumab group experienced events occurring during infusion, one event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the 12-week controlled trial experience, 16% of patients in the tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the tocilizumab group, the events included, but were not limited to rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events (urticaria) was considered serious.

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

Injection Site Reactions (ISRs)

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

Immunogenicity

In Study WA18221, all 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. In Study WA28118, 46 of the 51 (90.2%) patients tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post-baseline.

2.6.1.1 Laboratory Abnormalities

Hematology Abnormalities

Neutrophils

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

Rheumatoid Arthritis:

Intravenous Administration:

In the 6-month controlled trials decreases in neutrophil counts below 1 × 10^9/l occurred in 3.4% of patients on tocilizumab 8 mg/kg+DMARD compared to below 0.1% of patients on placebo+DMARD. Approximately half of the instances of ANC below 1 × 10^9/l occurred within 8 weeks of starting therapy. Decreases below 0.5 × 10^9/l were reported in 0.3% patients receiving tocilizumab 8 mg/kg+DMARD (see sections 2.2 Dosage and Administration and 2.4.1 Warnings and Precautions).

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

Subcutaneous Administration:

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

Giant Cell Arteritis

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

Polyarticular Juvenile Idiopathic Arthritis:

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1 × 10^9/l occurred in 3.7% of patients treated with IV tocilizumab and 15.4% of patients treated with SC tocilizumab.

Systemic Juvenile Idiopathic Arthritis:

During routine laboratory monitoring in the 12-week controlled trial, a decrease in neutrophil counts below 1×10^9/l occurred in 7% of patients in the tocilizumab group, and in none in the placebo group.

In the open-label extension study (WA18221), decreases in neutrophil counts below 1 x 10^9/L, occurred in 15% of the IV tocilizumab group.

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

Platelets

Rheumatoid Arthritis:

Intravenous Administration:

In the 6-month controlled trials decreases in platelet counts below 100×10^3/µl occurred in 1.7% of patients on tocilizumab 8 mg/kg plus traditional DMARDs compared to below 1% of patients on placebo plus traditional DMARDs, without associated bleeding events (see sections 2.2 Dosage and Administration and 2.4.1 Warnings and Precautions).

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

Subcutaneous Administration:

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

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, one patient (1%, 1/100) in the tocilizumab SC weekly group had a single transient occurrence of decreased platelet count below 100 x 103 / µL without associated bleeding events. A decrease in platelet count below 100 x 103 / µL was not observed in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis:

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

Systemic Juvenile Idiopathic Arthritis:

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

In the open-label extension study (WA18221), decreases in platelet counts below 100 x 10^3 / µL occurred in 3% of patients of the IV tocilizumab group, without associated bleeding events.

In the 52-week open-label trial (Study WA28118), decreases in platelet counts below 100×10^3 / µL occurred in 2% of patients treated with SC tocilizumab.

Liver enzyme elevations

Rheumatoid Arthritis:

Intravenous Administration:

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

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

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

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

Subcutaneous Administration:

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

Giant Cell Arteritis

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

Polyarticular Juvenile Idiopathic Arthritis:

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

Systemic Juvenile Idiopathic Arthritis:

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

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

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

Elevations in lipid parameters

Rheumatoid Arthritis:

Intravenous Administration:

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

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

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

Subcutaneous Administration:

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

Giant Cell Arteritis

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

Polyarticular Juvenile Idiopathic Arthritis:

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

Systemic Juvenile Idiopathic Arthritis:

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

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

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

2.6.1.1 Laboratory abnormalities-COVID-19

Intravenous Administration:

The incidence of laboratory abnormalities was generally similar between patients with COVID-19 who received one or two doses of tocilizumab compared with those who received placebo in studies ML42528, WA42380, and WA42511 with few exceptions. Decreases in platelets and neutrophils and elevations of ALT and AST were more frequent among patients receiving tocilizumab versus placebo

2.6.2 Post Marketing Experience

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

Table 3: Adverse drug reactions from post marketing experience

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

Hepatic failure	0.004 per 100 patient years	Very Rare	
Jaundice[3]	Not observed in clinical trials	Rare	

[1] See section 2.3 Contraindications

[2] See section 2.4.1 Warnings and Precautions, General

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

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

2.7 Overdose

There are limited data available on overdosage with tocilizumab. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg IV. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg IV, although dose-limiting neutropenia was observed.

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

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

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

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

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

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

The effect of tocilizumab on CYP enzymes (except CYP2C19 and CYP2D6 [36]) is clinically relevant for CYP450 substrates with a narrow therapeutic index, and/or where the dose is individually adjusted.

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

When starting or stopping therapy with tocilizumab, patients taking medicinal products, which are individually dose-adjusted and are metabolised via CYP450 3A4, 1A2, or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses of these products may need to be adjusted to maintain their

therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

3 PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.6 Pharmacodynamic Properties

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

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

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to their lowest 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose-dependent manner. Rheumatoid arthritis and GCA patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see section 2.4.1 Warnings and Precautions, General).

In COVID-19 patients with one dose of tocilizumab 8 mg/kg administered intravenously, decreases in the levels of CRP to within normal ranges were seen as early as Day 7

3.6.1 Mechanism of Action

Tocilizumab is a recombinant humanised anti-human interleukin6 (IL6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass. Tocilizumab binds to both soluble and membrane-bound IL6 receptors (sIL6R and mIL6R), and has been shown to inhibit sIL6R and mIL6R-mediated signaling. IL-6 is a multifunctional cytokine, produced by a variety of cell types involved in local paracrine function as well as in the regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute-phase proteins and stimulation of hematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis, and neoplasia.

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

3.6.2 Clinical / Efficacy Studies

Rheumatoid Arthritis

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

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

Study I evaluated 673 patients who had not been treated with MTX within 6 months prior to 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 to a maximum of 20 mg weekly over an 8-week period). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study II, a 2-year study, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks as blinded therapy for 52 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved ACR20 response criteria. At week 52 the co-primary endpoints were prevention of joint damage and improvement in physical function.

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

The percent of patients achieving ACR20, 50 and 70 responses in Studies I to V is shown in Table 4.

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

Study SC-I evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s). Approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomised 1:1 to receive tocilizumab SC 162 mg every week or tocilizumab IV 8 mg/kg every four weeks in combination with non-biologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results from study SC-I is shown in Table 6.

Table 4ACR Responses in MTX/Placebo-Controlled Trials (Percent of Patients)

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

TCZ = tocilizumab
* p<0.05, tocilizumab vs. placebo+MTX/DMARD
** p<0.01, tocilizumab vs. placebo+MTX/DMARD
*** p<0.0001, tocilizumab vs. placebo+MTX/DMARD
† MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more.

In all studies, 8 mg/kg tocilizumab-treated patients had statistically significant higher ACR20, 50, 70 response rates at 6 months compared to control. The treatment effect was similar in patients independent of rheumatoid-factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the open-label extension studies of Studies I–V.

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

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

Table 5: Cross-Study Comparison of DAS and EULAR Responses at Week 24

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

TCZ = tocilizumab

† The p value compares across all the EULAR categories

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

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

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

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

Table 6 Clinical Response at Week 24 in Subcutaneous Trial (Percent of Patients)

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

Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	
Change in DAS28 [adjusted mean]		
Week 24	3.5	3.5
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)	
DAS28 < 2.6		
Week 24	38.4%	36.9%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)	
EULAR response (%)		
None	3.3%	4.8%
Moderate	41.7%	42.7%
Good	55.0%	52.4%

TCZ = tocilizumab
a = Per Protocol Population

Major Clinical Response

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

Radiographic Response - Intravenous Administration

In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving tocilizumab compared to control.

In the open-label extension of Study II the inhibition of progression of structural damage in tocilizumab/MTX-treated patients was maintained in the second year of treatment.

Table 7Radiographic mean changes at 52 and 104 weeks in Study II

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

PBO - Placebo
MTX - Methotrexate
TCZ - Tocilizumab
JSN - Joint space narrowing

All data presented was read together in campaign 2 which consists of the evaluations of the baseline, week 24, week 52, week 80, week 104 and early withdrawal or escape therapy readings taken up to week 104 visit

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

Radiographic Response – Subcutaneous Administration

The radiographic response of subcutaneously administered tocilizumab was assessed in a double-blind, controlled, multicenter study in patients with active RA. This study (SC-II) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. Patients were required to be above 18 years of age with active rheumatoid arthritis diagnosed according to ACR criteria and who had at least 8 tender and 6 swollen joints at baseline. In SC-II, 656 patients were randomised 2:1 to tocilizumab SC 162 mg every other week or placebo, in combination with non-biologic DMARD(s).

In study SC-II, inhibition of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified mean total Sharp score (mTSS). At week 24, inhibition of structural damage was shown, with significantly less radiographic progression in patients receiving tocilizumab SC compared with placebo (mTSS of 0.62 vs. 1.23, p=0.0149 (van

Elteren). These results are consistent with those observed in patients treated with intravenous tocilizumab.

Quality-of-Life Outcomes – Intravenous Administration

Clinically significant improvements in disability index (HAQ-DI, Health Assessment Questionnaire Disability Index), fatigue (FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue) and improvement in both the physical (PCS, Physical Component Summary) and mental health (MCS, Mental Component Summary) domains of the SF-36 (Short Form 36) were observed in patients treated with 8 mg/kg tocilizumab (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs (Table 6).

At week 24, the proportion of 8 mg/kg tocilizumab-treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of > 0.25), was significantly higher than among patients receiving placebo + MTX/DMARDs in all studies. During the open-label period of Study II the improvement in physical function was maintained for up to 2 years.

Table 8 Comparison of SF-36, HAQ and FACIT-Fatigue Responses at Week 24

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

TCZ = tocilizumab
* p<0.05, tocilizumab vs. placebo+MTX/DMARD
** p<0.01, tocilizumab vs. placebo+MTX/DMARD
*** p<0.0001, tocilizumab vs. placebo+MTX/DMARD

In Study II, changes in PCS, MCS and FACIT-Fatigue at 52 weeks were 10.1***, 5.4 and 8.4**, respectively, in the TCZ 8 mg/kg + MTX group compared to 5.6, 3.8 and 5.5, respectively, in the placebo plus MTX group. At Week 52, the mean change in HAQ-DI was -0.58 in the TCZ 8 mg/kg

+ MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the TCZ 8 mg/kg + MTX group (-0.61).

Quality of Life Outcomes – Subcutaneous Administration

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

Laboratory Evaluations

Treatment with 8 mg/kg tocilizumab in combination with DMARD/MTX or as monotherapy resulted in a highly statistically significant improvement in hemoglobin levels compared with placebo + MTX/DMARD ($p<0.0001$) at week 24. The greatest improvement was observed in patients with chronic anemia associated with RA; mean hemoglobin levels increased by week 2 and remained within normal range through week 24.

A marked decrease in mean levels of acute-phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after tocilizumab administration. Consistent with the effect on acute-phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range.

MTX-Naïve, Early RA

Study VI, a 2-year study with the planned primary analysis at week 52 evaluated 1162 MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months). This study evaluated the efficacy of i.v. tocilizumab 4 or 8 mg/kg every 4 weeks/MTX combination therapy, i.v. tocilizumab 8 mg/kg monotherapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage for 104 weeks. The primary endpoint was the proportion of patients achieving DAS28 remission (DAS28 below 2.6) at week 24. A significantly higher proportion of patients in the tocilizumab 8 mg/kg + MTX and tocilizumab monotherapy groups met the primary endpoint compared with MTX alone. The tocilizumab 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the tocilizumab 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints. In this study, ACR/EULAR remission (Boolean and Index) were also analysed as pre-specified exploratory endpoints, with higher responses observed in the tocilizumab groups. The results from Study VI are shown in Table 7.

Table 9: Efficacy Results for Study VI (WA19926) on MTX-Naïve, Early RA Patients

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

All efficacy comparisons vs placebo + MTX. ***p≤0.0001; **p<0.001; *p<0.05;

‡p-value < 0.05 vs. placebo + MTX, but endpoint was exploratory (not included in the hierarchy of statistical testing and has therefore not been controlled for multiplicity).

Monotherapy: tocilizumab versus adalimumab

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

A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 8).

Table 10 Efficacy Results for Study WA 19924

	ADA + Placebo (IV) N = 162	**TCZ + Placebo (SC) N = 163**	p-value[(a)]
Primary Endpoint - Mean Change from Baseline at Week 24			
DAS28 (adjusted mean)	**-1.8**	**-3.3**	
Difference in adjusted mean (95% CI)	**-1.5 (-1.8, -1.1)**		**<0.0001**
Secondary Endpoints - Percentage of Responders at Week 24 [(b)]			
DAS28 < 2.6, N (%)	18 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, N (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, N (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, N (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, N (%)	29 (17.9)	53 (32.5)	0.0023

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

Cardiovascular Outcomes

Study WA25204 was a randomized, open-label (sponsor-blinded), 2-arm parallel-group, multicenter, non-inferiority, cardiovascular (CV) outcomes trial in patients with a diagnosis of moderate to severe RA. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with TCZ compared with a TNF inhibitor standard of care (etanercept [ETA]).

The study included 3,080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying anti-rheumatic drugs, who were aged ≥50 years with at least one additional CV risk factor beyond RA. Patients were randomized 1:1 to IV TCZ 8 mg/kg Q4W or

SC ETA 50 mg QW and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events reviewed by an independent and blinded adjudication committee.

Non-inferiority of TCZ to ETA for cardiovascular risk was determined by excluding a >80% relative increase in the risk of MACE. The primary endpoint was met such that a >43% increase in the risk of MACE could be excluded (hazard ratio [HR] comparing TCZ to ETA = 1.05; 95% CI = 0.77, 1.43).

Giant Cell Arteritis (GCA)

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

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

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

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

The primary efficacy endpoint, assessed by the proportion of patients achieving steroid-free sustained remission at Week 52 on tocilizumab plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 9).

The key secondary efficacy endpoint, also based on the proportion of patients achieving sustained remission at Week 52, comparing tocilizumab plus 26 weeks prednisone taper with the longer placebo plus 52 weeks prednisone taper, was also met (Table 9).

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

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

Secondary Endpoints

The assessment of the time to first GCA flare showed a significantly lower risk of flare for the tocilizumab SC weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the tocilizumab SC every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). Tocilizumab SC weekly dose also showed a clinically meaningful decrease in the risk for flare compared to

placebo plus 26 weeks prednisone in patients who entered the trial with relapsing GCA as well as those with new-onset disease (Table 9).

Cumulative glucocorticoid dose

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

Table 11: Efficacy Results from Study WA28119

	PBO + 26 weeks prednisone taper N=50	PBO + 52 weeks prednisone taper N=51	TCZ 162mg SC QW + 26 weeks prednisone taper N=100	TCZ 162 mg SC Q2W + 26 weeks prednisone taper N=49
Primary Endpoint				
Sustained remission (TCZ groups vs PBO+26)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	42%* (18.00, 66.00)	39.06%* (12.46 , 65.66)
Key Secondary Endpoint				
Sustained remission (TCZ groups vs PBO+52)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	38.35%* (17.89 , 58.81)	35.41%** (10.41 ,60.41)
Other Secondary Endpoints				

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

* p<0.0001
** p<0.005 (threshold for significance for primary and key secondary tests of superiority)
*** descriptive p value <0.005
[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
TCZ: Tocilizumab
PBO: Placebo
QW: every week dose
Q2W: every other week dose

Quality of Life Outcomes

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

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

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

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

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

COVID-19

RECOVERY (Randomised Evaluation of COVID-19 Therapy) Collaborative Group Study in Hospitalized Adults Diagnosed with COVID-19

RECOVERY was a large, randomized, controlled, open-label, multi-center platform study conducted in the United Kingdom to evaluate the efficacy and safety of potential treatments in hospitalized adult patients with severe COVID-19. All eligible patients received usual care and underwent an initial (main) randomization. Eligible patients for the trial had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical contraindications to any of the treatments. Patients with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) qualified for a second randomization to receive either intravenous tocilizumab or usual care alone.

Efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 patients who were randomized with 2022 patients in the tocilizumab + usual care arm and 2094 patients in the usual care alone arm. The baseline demographic and disease characteristics of the ITT population were well balanced across treatment arms. The mean age of participants was 63.6 years (standard deviation [SD] 13.6 years). The majority of patients were male (67%) and White

(76%).The median (range) level of CRP was 143 mg/L (75-982). At baseline, 0.2%(N=9) of patients were not on supplemental oxygen, 45% of patients required low flow oxygen, 41% of patients required non-invasive ventilation or high-flow oxygen and 14% of patients required invasive mechanical ventilation; 82% of patients were receiving systemic corticosteroids. The most common comorbidities were diabetes (28.4%), heart disease (22.6%) and chronic lung disease (23.3%).

The primary outcome was time to death through Day 28. The hazard ratio comparing the tocilizumab + usual care arm to the usual care alone arm was 0.85 (95% CI: 0.76 to 0.94), a statistically significant result (p=0.0028). The probabilities of dying by Day 28 were estimated to be 30.7% and 34.9% in the tocilizumab and usual care arms, respectively. The risk difference was estimated to be -4.1% (95% CI: -7.0% to -1.3%), consistent with the primary analysis. The hazard ratio among the pre-specified subgroup of patients receiving systemic corticosteroids at baseline was 0.79 (95% CI: 0.70 to 0.89), and for the pre-specified subgroup not receiving systemic corticosteroids at baseline was 1.16 (95% CI: 0.91 to 1.48).

The median time to hospital discharge was 19 days in the tocilizumab + usual care arm and >28 days in the usual care arm (hazard ratio [95% CI] = 1.22 [1.12 to 1.33]).

Among patients not requiring invasive mechanical ventilation at baseline, the proportion of patients who required mechanical ventilation or died by Day 28 was 35% (619/1754) in the tocilizumab + usual care arm and 42% (754/1800) in the usual care alone arm (risk ratio [95% CI] = 0.84, [0.77 to 0.92] p<0.0001).

Study ML42528 (EMPACTA)

Study ML42528 was a global Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous tocilizumab in combination with standard of care (SoC), in hospitalized, non-ventilated adult patients with COVID-19 pneumonia. Eligible patients were at least 18 years of age, had confirmed SARS-CoV-2 infection by a positive reverse transcriptase polymerase chain reaction (RT-PCR) result, had pneumonia confirmed by radiography, and had SpO2 < 94% on ambient air. Standard of care may have included antiviral treatment, low dose systemic corticosteroids, and supportive care. Patients were randomized at a 2:1 ratio to receive one infusion of either 8 mg/kg tocilizumab with a maximum dose of 800 mg, or placebo. If the clinical signs or symptoms worsened or did not improve, one additional infusion of blinded treatment of tocilizumab or placebo could be given, 8–24 hours after the initial infusion.

Of the 389 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of patients who received any amount of study medication (249 in the tocilizumab arm; 128 in the placebo arm). The baseline demographic and disease characteristics were overall balanced across treatment arms. In the mITT population (n=377) at randomization, median age was 57 years (range 20-95); 59.2% of patients were male, 56% were of Hispanic or Latino ethnicity, 52.8% were White, 20.4% were American Indian/Alaska Native, 15.1% were Black/African American and 1.6% were Asian. At baseline, 35 (9.3%) patients were

not on supplemental oxygen, 242 (64.2%) patients required low flow oxygen and 100 (26.5%) patients required high-flow oxygen. The median time from symptom onset was 8.0 days. At baseline, across treatment arms, 72.7% of patients received systemic corticosteroids and 47.7% received remdesivir. The median (range) levels of CRP and ferritin were, respectively, 136.10 mg/L (2.5-3776.0), and 1.4 pmol/mL (0.03-122.3). The most common comorbidities were hypertension (48.3%), diabetes (40.6%), hyperlipidemia (27.6%) and obesity (24.4%).

The primary efficacy endpoint was the cumulative proportion of patients who required mechanical ventilation or died by Day 28. For patients who received tocilizumab, there was a statistically significant improvement in the time to progression to mechanical ventilation or death compared to patients who received placebo (log-rank p value = 0.0360; HR [95% CI] = 0.56 [0.33 to 0.97]). The cumulative proportion of patients requiring mechanical ventilation or who died by Day 28 estimated by Kaplan-Meier method was 12.0% (95% CI, 8.52% to 16.86%) in the tocilizumab arm and 19.3% (95% CI, 13.34% to 27.36%) in the placebo arm.

The median time to hospital discharge or "ready for discharge" to Day 28 was 6.0 days in the tocilizumab arm and 7.5 days in the placebo arm (HR=1.16 [95% CI, 0.91 to 1.48]).

Mortality at Day 28 was 10.4% in the tocilizumab arm versus 8.6% in the placebo arm (weighted difference (tocilizumab arm - placebo arm): 2.0% [95% CI, -5.2% to 7.8%]). Mortality at Day 60 (post-hoc analysis) was 11.2% in the tocilizumab arm versus 10.9% in the placebo arm (weighted difference (tocilizumab arm - placebo arm): 0.5% [95% CI, -6.9% to 6.8%])

Study WA42380 (COVACTA)

Study WA42380 was a global Phase III, randomized, double-blind, placebo-controlled, multi-centre study to assess the efficacy and safety of intravenous tocilizumab, in combination with standard of care (SoC), in adult patients hospitalized with severe COVID-19 pneumonia. Eligible patients were at least 18 years of age, had confirmed SARS-CoV-2 infection by a positive RT-PCR result, had pneumonia confirmed by radiography, and had oxygen saturation of 93% or lower on ambient air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less. SOC may have included antiviral treatment, low-dose corticosteroids, convalescent plasma and other supportive therapies. Patients were randomized at a 2:1 ratio to receive one infusion of either 8 mg/kg tocilizumab, with a maximum dose of 800 mg, or placebo. If clinical signs or symptoms worsened or did not improve, one additional infusion of blinded treatment of tocilizumab or placebo could be given, 8–24 hours after the initial infusion.

Of the 452 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of patients who received any amount of study medication (294 in the tocilizumab arm; 144 in the placebo arm). The baseline demographic and disease characteristics were overall balanced across treatment arms. For the overall mITT population (n=438) at randomization, median age was 62 years (range 22-96 with 44.3% of patients aged 65 or older); 69.9% of patients were male, 32.2% were of Hispanic or Latino ethnicity, 57.5% were White, 15.1% were Black/African American and 8.7% were Asian. At baseline, 3.4% of patients were not on supplemental oxygen, 27.9% were on low flow oxygen, 30.4% were on non-invasive ventilation or high flow oxygen, and 38.4% were on invasive mechanical ventilation. The median

time from symptom onset was 11.0 days. At baseline, across treatment arms, 22.4% patients received systemic corticosteroids and 5.7% received remdesivir. The median (range) levels of IL-6, CRP and ferritin were, respectively, 85.8 ng/L (3.1-4020), 155.15 mg/L (1.1-499.6), and 2.20 pmol/mL (0.0-75.3). The most common comorbidities were hypertension (62.1%), diabetes (38.1%), cardiovascular impairment (28.1%) and obesity (20.5%).

The primary efficacy endpoint was clinical status on Day 28 assessed on a 7-category ordinal scale consisting of the following categories:

1. Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen);

2. Non–ICU hospital ward (or "ready for hospital ward"), not requiring supplemental oxygen;

3. Non–ICU hospital ward (or "ready for hospital ward"), requiring supplemental oxygen;

4. ICU or non–ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen;

5. ICU, requiring intubation and mechanical ventilation;

6. ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy);

7. Death Study

There was no statistically significant difference observed in the distribution of clinical status on the 7-category ordinal scale at Day 28 when comparing the tocilizumab arm to the placebo arm. The median clinical status category at Day 28 was 1.0 in the tocilizumab arm and 2.0 in the placebo arm (odds ratio (OR) 1.19 [95% CI: 0.81, 1.76]).

The median time to hospital discharge or "ready for discharge" to Day 28 was 20 days in the tocilizumab arm and 28 days in the placebo arm (HR=1.35 [95% CI, 1.02 to 1.79]).

Mortality at Day 28 was 19.7% in the tocilizumab arm versus 19.4% in the placebo arm (weighted difference (tocilizumab arm - placebo arm) Day 28: 0.3% [95% CI, -7.6 to 8.2]. Mortality at Day 60 was 24.5% in the tocilizumab arm versus 25.0% in the placebo arm (weighted difference (tocilizumab arm - placebo arm): -0.5% [95% CI, -9.1 to 8.0]).

Mortality at Day 60 was 24.5% in the tocilizumab arm versus 25.0% in the placebo arm (weighted difference (tocilizumab arm - placebo arm): -0.5% [95% CI, -9.1 to 8.0])

Study WA42511 (REMDACTA)

Study WA42511 was a global, Phase III, randomized, double-blind, placebo-controlled, multicenter study conducted to assess the efficacy and safety of intravenous tocilizumab in combination with remdesivir (RDV) compared with matching placebo in combination with RDV in hospitalized adult patients with severe COVID-19 pneumonia. Eligible patients were at least 12 years of age with confirmed SARS-CoV-2 infection, including a positive polymerase chain reaction (PCR) and pneumonia confirmed by radiography, and required supplemental oxygen > 6 L/min to maintain SpO2 >93%. Patients were randomized at a 2:1 ratio to receive blinded treatment of either

tocilizumab + RDV or a matching placebo + RDV. Study treatment was given in combination with standard of care per local guidance (e.g corticosteroids, supportive care). Patients assigned to the tocilizumab + RDV arm received one infusion of tocilizumab 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo +RDV arm received one infusion of placebo. For both arms, if the clinical signs or symptoms worsened or did not improve one additional infusion of blinded treatment of tocilizumab or placebo could be given, 8–24 hours after the initial infusion.

Of the 649 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of all patients who received any amount of tocilizumab / placebo (430 in the tocilizumab +RDV arm; 210 in the placebo+RDV arm). The baseline demographic and disease characteristics were overall balanced across treatment arms. For the overall mITT population (n=640) at randomization, median age was 60 years (range 20-93 years with 38.3% of patients aged 65 or older); 63.3% of patients were male, 51.6% were Hispanic or Latino, 67% were White, 10.9% were Black/African American and 3.4% were Asian. At baseline, 6.6% were on low flow oxygen, 79.8% were on non-invasive ventilation or high flow oxygen and 13.6% were on invasive mechanical ventilation. The median time from symptom onset was 8 days. At baseline, the majority of patients received corticosteroids (84.2% across treatment arms). The median (range) levels of CRP and ferritin were 98.20 mg/L (1.3 - 418.3) and 2.13 pmol/mL (0.1-30.8), respectively. The most common comorbidities were hypertension (61.7%), diabetes (39.5%) and obesity (27%).

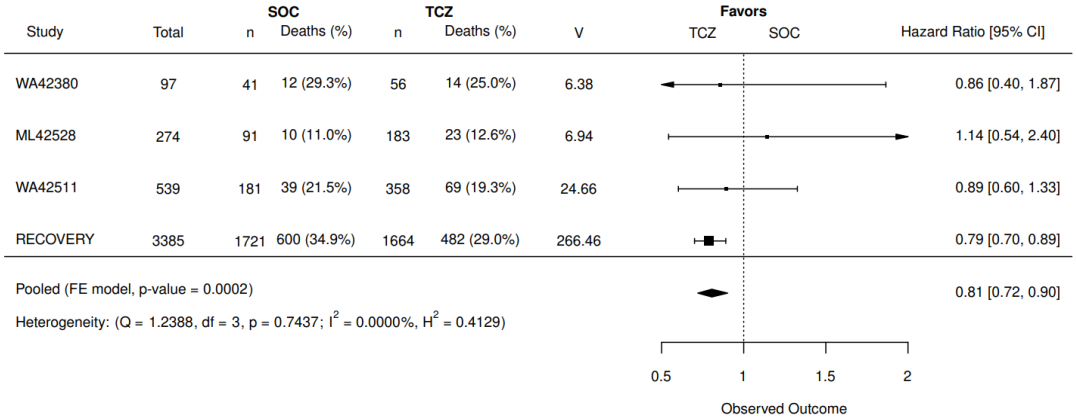
The primary efficacy endpoint was time from randomization to hospital discharge or “ready for discharge” up to Day 28. There was no statistically significant difference observed between treatment arms with respect to time to hospital discharge or “ready for discharge” through Day 28 (HR 0.965 [95% CI: 0.78 to 1.19]) or time to mechanical ventilation or death through Day 28 (HR 0.980 [95% CI: 0.72 to 1.34]).

Mortality at Day 28 was 18.1% in the tocilizumab arm versus 19.5% in the placebo arm (weighted difference (tocilizumab arm - placebo arm): -1.3% [95% CI, -7.8% to 5.2%]). Mortality at Day 60 was 22.6% in the tocilizumab arm versus 25.7% in the placebo arm (weighted difference (tocilizumab arm - placebo arm): -3.0% [95% CI, -10.1% to 4%]).

Meta-analysis of RECOVERY, EMPACTA (Study ML42528), COVACTA (Study WA42380) and REMDACTA (Study WA42511) by Baseline Systemic Corticosteroid Treatment

A study-level meta-analysis was conducted on the 3 Roche trials and the RECOVERY study. For each study, the hazard ratio (HR) for time to death up to Day 28 was estimated in the subgroup of patients receiving baseline systemic corticosteroids (tocilizumab: 597 and placebo: 313 from Roche trials, tocilizumab: 1664 and standard of care 1721 from RECOVERY). The combined HR showed that tocilizumab treatment (n=2261) resulted in a 19% relative reduction in the risk of death up to Day 28 (HR=0.81; 95% CI: 0.72, 0.90; p=0.0002) compared to SoC (n=2034).

Figure 1 Meta analysis of Time to Death up to Day 28 for Baseline Corticosteroid Use Subpopulation



Cox hazard ratio (HR) for Roche Trials. Log-rank O-E for RECOVERY
where HR calculated by taking ln(HR) to be (O-E)/V with normal variance 1/V.
A fixed effects model with ln(HR) as response and V as the weights to get the pooled effect.
Roche Data Source:
root/clinical_studies/RO4877533/share/pool_COVID19/prod/outdata_vad

Polyarticular Juvenile Idiopathic Arthritis

The efficacy of intravenous tocilizumab was assessed in a three-part study including an open-label extension in children with active polyarticular juvenile idiopathic arthritis (pJIA). Part I consisted of a 16-week active tocilizumab treatment lead-in period (N=188) followed by Part II, a 24-week randomised double-blind placebo-controlled withdrawal period (ITT, N=163), followed by Part III, a 64-week open-label period. Eligible patients ≥ 30 kg received tocilizumab at 8 mg/kg for 4 doses. Patients below 30 kg were randomised 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg i.v. every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline entered the blinded withdrawal period (Part II) of the study. In Part II, patients were randomised to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR30 flare at Week 40 relative to Week 16. Forty-eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of TCZ-treated patients. These proportions were statistically significantly different (p=0.0024).

At the conclusion of Part I, JIA ACR30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.

During the withdrawal phase (Part II), the percent of patients achieving JIA ACR30, 50, and 70 responses at Week 40 relative to baseline is shown in the table below.

Table 12 JIA ACR Response Rates at Week 40 Relative to Baseline (Percent of Patients)

Response Rate	**TCZ** **N=82**	**Placebo** **N=81**

JIA ACR30	74.4%†	54.3%†
JIA ACR50	73.2%†	51.9%†
JIA ACR70	64.6%†	42.0%†

† p<0.01, tocilizumab vs. placebo

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

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

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

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

Systemic Juvenile Idiopathic Arthritis

The efficacy of intravenous tocilizumab for the treatment of active sJIA was assessed in a 12-week randomised, double-blind, placebo-controlled, parallel-group, 2-arm study. Patients (treated with or without MTX) were randomised (TCZ:placebo = 2:1) to one of two treatment groups, 75 patients received tocilizumab infusions every two weeks either 8 mg/kg for patients ≥30 kg or 12 mg/kg for patients < 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the open-label extension phase at weight-appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30 response) at Week 12 and absence of fever (no temperature recording ≥ 37.5°C in the preceding 7 days). Eighty-five percent (64/75) of the patients treated with TCZ and 24.3% (9/37) of placebo patients achieved this endpoint. These proportions were highly significantly different (p<0.0001).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in Table 11. Responses are maintained in the open-label extension.

Table 13 JIA ACR Response Rates at Week 12 (Percent of Patients)

Response Rate	**TCZ**	**Placebo**

	N=75	**N=37**
ACR30	90.7%*	24.3%
ACR50	85.3%*	10.8%
ACR70	70.7%*	8.1%
ACR90	37.3%*	5.4%

* p<0.0001, tocilizumab vs. placebo

Systemic Features

In those patients treated with tocilizumab, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording ≥ 37.5°C in the preceding 14 days) at Week 12 versus only 21% of placebo patients (p<0.0001) and 64% of tocilizumab-treated patients with rash characteristic of sJIA at baseline were free of rash at Week 12 versus 11% of placebo patients (p=0.0008).

There was a highly statistically significant reduction in pain for tocilizumab-treated patients at Week 12 in comparison to placebo patients. The adjusted mean change in the pain VAS after 12 weeks of tocilizumab treatment was a reduction of 41 points on a scale of 0 to 100 compared to a reduction of 1 for placebo patients (p<0.0001).

The responses for systemic features are maintained in the ongoing open-label extension.

Corticosteroid Tapering

Of the 31 placebo and 70 tocilizumab patients receiving oral corticosteroids at baseline, 8 placebo and 48 tocilizumab patients achieved a JIA ACR70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) tocilizumab patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroids by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to Week 12 (p=0.028). Reductions in corticosteroids continued, with 44 patients off oral corticosteroids, at week 44, while maintaining ACR responses.

Quality of Life

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

Laboratory Parameters

Fifty out of seventy-five (67%) patients treated with tocilizumab had a hemoglobin below LLN at baseline. Forty (80%) of these patients with decreased hemoglobin had an increase in their hemoglobin to within the normal range at week 12, in comparison to only 2 out of 29 (7%) of placebo patients with hemoglobin <below LLN at baseline (p<0.0001). Forty-four (88%) tocilizumab patients with decreased hemoglobin at baseline had an increase in their hemoglobin by ≥ 10 g/l at week 6 versus 1 (3%) placebo patient (p<0.0001).

The proportion of tocilizumab-treated patients with thrombocytosis at baseline who had a normal platelet count at week 12 was significantly higher than in the placebo patients, 90% versus 4% (p<0.0001).

A marked decrease in mean levels of acute-phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after tocilizumab administration.

A Phase I, multi-centre, open-label, single arm study (NP25737) to evaluate the PK, safety and exploratory PD and efficacy of tocilizumab over 12 weeks in paediatric sJIA patients (N=11) under 2 years of age was conducted [95]. Patients (treated with stable background therapy of corticosteroids, MTX, or non-steroidal anti-inflammatory drugs) received intravenous tocilizumab 12 mg/kg every two weeks. Patients who completed the 12-week period could continue to the optional extension period (a total of 52-weeks or until the age of 2 years, whichever was longer).

The primary PK endpoints (Cmax, Cmin and AUC2weeks) of TCZ at steady-state in this study are within the ranges of these parameters observed in paediatric patients aged 2 to 17 years in Study WA18221.

The types of AEs observed during the 12-week evaluation period of Study NP25737 were consistent with the safety profile observed in the pivotal Phase III study (WA18221). Of the 11 patients aged under 2 years, three experienced serious hypersensitivity reactions, and three developed treatment induced anti-tocilizumab antibodies after the event. However, due to the small sample size, the low number of events and confounding factors, conclusions could not be drawn.

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

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

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

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

3.2 Pharmacokinetic Properties

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

Rheumatoid Arthritis

The pharmacokinetics in healthy subjects and RA patients suggest that PK is similar between the two populations.

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

Table 14: Predicted mean ± SD PK parameters at steady-state after IV and SC dosing in RA

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

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

At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal half-life of approximately 21.5 days was derived from the population parameter estimates.

While after IV administration maximum concentration (C_{max}) increased dose-proportionally between doses of 4 and 8 mg/kg IV every 4 weeks, a greater than dose-proportional increase was observed in the average concentration (C_{mean}) and trough concentration (C_{trough}). At steady-state, C_{mean} and C_{trough} were 3.2 and 32 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively [74,88]. Exposures after the 162 mg SC QW regimen were greater by 4.6 (C_{mean}) to 7.5 fold (C_{trough}) compared to the 162 SC Q2W regimen.

The accumulation ratios for AUC and C_{max} after multiple doses of 4 and 8 mg/kg Q4W are low, while the accumulation ratios are higher for C_{trough} (2.62 and 2.47). Accumulation ratios after multiple doses of either SC regimen were higher than after IV regimen with the highest ratios for C_{trough} (6.02 and 6.30). The higher accumulation for C_{trough} was expected based on the nonlinear clearance contribution at lower concentrations.

For C_{max}, more than 90% of the steady-state was reached after the 1st IV infusion, and after the 12th SC and the 5th SC injection in QW and Q2W regimens respectively. For AUC_{τ} and C_{mean}, 90% of the steady-state was reached after the 1st and 3rd infusion for the 4 mg/kg and 8 mg/kg IV, respectively, and after the 6th and 12th injections for the 162 mg SC Q2W and QW regimens respectively. For C_{trough}, approximately 90% of the steady-state was reached after the 4th IV infusion, the 6th and 12th injections for the respective SC regimens.

Population PK analysis identified body weight as a significant covariate impacting pharmacokinetics of tocilizumab. When given IV on a mg/kg basis, individuals with body weight ≥ 100 kg are predicted to have mean steady-state exposures higher than mean values for the patient population [74,88]. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see section 2.2 Dosage and Administration) [46]. Due to the flat dosing employed for SC administration of tocilizumab, no modifications are necessary by this dosing route.

Giant Cell Arteritis (GCA)

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

Table 15: Predicted mean ± SD PK parameters at steady-state after SC dosing in GCA

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

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

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

COVID-19

The pharmacokinetics of tocilizumab in COVID-19 adult patients was characterized in Study WA42380 (COVACTA) and Study CA42481 (MARIPOSA) by a population pharmacokinetic analysis which included 380 adult patients who were treated with one or two 8mg/kg IV infusions administered at least 8 hours apart .

Table 16. Predicted mean ± (SD) PK parameters after 8 mg/kg IV dosing in COVID-19

	8 mg/kg	
TCZ PK Parameter	**One dose**	**Two doses**
C_{max} (mcg/mL)	154 (34.9)	296 (64.7)
C_{day28} (mcg/mL)	0.934 (1.93)	8.94 (8.5)

Population PK analysis identified body weight and disease severity as significant covariates impacting pharmacokinetics of intravenous tocilizumab. With a dosing regimen of 8 mg/kg tocilizumab with a maximum dose of 800 mg tocilizumab, within a specified Ordinal Scale (OS) category, compared to patients with a mean body weight of 80 kg, exposure was 20% lower in patients weighing less than 60 kg. Exposure in patients weighing more than 100 kg was in the same range as exposure in patients with a mean body weight of 80 kg. For an 80 kg patient, exposure decreased as disease severity increased; for each category increase on the OS, exposure decreased consistently by 13%.

Polyarticular Juvenile Idiopathic Arthritis

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

Table 17. Predicted mean ± SD PK parameters at steady-state after IV or SC dosing in pJIA

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

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

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

Systemic Juvenile Idiopathic Arthritis

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

Table 18. Predicted mean ± SD PK parameters at steady-state after IV or SC dosing in sJIA

	IV		SC	
TCZ PK Parameter	**8 mg/kg Q2W ≥ 30 kg**	**12 mg/kg Q2W below 30 kg**	**162 mg QW ≥ 30 kg**	**162 mg Q2W below 30 kg**
C_{max} (µg/mL)	256 ± 60.8	274 ± 63.8	99.8 ± 46.2	134 ± 58.6
C_{trough} (µg/mL)	69.7 ± 29.1	68.4 ± 30.0	79.2 ± 35.6	65.9 ± 31.3
C_{mean} (µg/mL)	119 ± 36.0	123 ± 36.0	91.3 ± 40.4	101 ± 43.2
Accumulation C_{max}	1.42	1.37	3.66	1.88
Accumulation C_{trough}	3.20	3.41	4.39	3.21
Accumulation C_{mean} or AUC_{τ} *	2.01	1.95	4.28	2.27

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

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

The pharmacokinetics of tocilizumab were similar in paediatric patients under 2 years compared to patients over 2 years of age with a body weight below 30 kg from a regimen of 12 mg/kg IV tocilizumab given every 2 weeks.

3.2.1 Absorption

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

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

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

3.2.2 Distribution

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

In 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

In pediatric patients with pJIA, the central volume of distribution was 1.98 l, the peripheral volume of distribution was 2.1 l, resulting in a volume of distribution at steady state of 4.08 l.

In 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.

In adult patients with COVID-19, the central volume of distribution was 4.52 L, the peripheral volume of distribution was 4.23 L resulting in a volume of distribution of 8.75 L

3.2.3 Metabolism

No text.

3.2.4 Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 ml/h in RA patients, 6.7 ml/h in GCA patients, 5.8 ml/h in pediatric patients with polyarticular juvenile idiopathic arthritis and 7.1 ml/h in pediatric patients with systemic juvenile idiopathic arthritis. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. Due to dependence of total clearance on tocilizumab serum concentrations, $t_{1/2}$ of tocilizumab is also concentration-dependent and can only be calculated at a given serum concentration level.

In RA patients, for intravenous administration, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 13days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal $t_{1/2}$ of approximately 21.5 days was derived from the population parameter estimates.

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

In adult patients with COVID-19, serum concentrations were below the limit of quantification after 35 days on average following one infusion of tocilizumab IV 8 mg/kg. The average linear clearance in the population pharmacokinetic analysis was estimated to be 17.6 mL/h in patients with baseline ordinal scale category 3 (OS 3, patients requiring supplemental oxygen), 22.5 mL/h in patients with baseline OS 4 (patients requiring high-flow oxygen or non-invasive ventilation), 29 mL/h in patients with baseline OS 5 (patients requiring mechanical ventilation), and 35.4 mL/h in patients with baseline OS 6 (patients requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support)

In children with pJIA the effective $t_{1/2}$ of tocilizumab is up to 17 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady-state. After subcutaneous administration, the effective t1/2 of tocilizumab in pJIA patients is up to 10 days for the two body weight categories (Q2W regimen for body weight ≥30 kg or Q3W regimen for body weight below< 30 kg) during a dosing interval at steady state.

In children with sJIA, the effective t1/2 of IV tocilizumab is up to 16 days for both the 12 mg/kg and 8 mg/kg Q2W regimens during a dosing interval at steady-state. Following subcutaneous administration, the effective t1/2 of tocilizumab in sJIA patients is up to 14 days for both the 162 mg QW and Q2W regimens during a dosing interval at steady state.

3.2.5 Pharmacokinetics in Special Populations

Hepatic Impairment

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

Renal Impairment

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

Most of the patients in the RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab. Approximately one-third of the patients in the study WA28119 had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on tocilizumab exposure was noted in these patients.

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

Other Special Populations

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

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

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

3.3.2 Genotoxicity

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

3.3.3 Impairment of Fertility

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

3.3.4 Reproductive Toxicity

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

3.3.5 Other

In an embryo-fetal toxicity study conducted in cynomolgus monkeys a slight increase of abortion/embryo-fetal death was observed with high systemic cumulative exposure (above 100

times human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. The abortion incidence was within the historical background for the cynomolgus monkey in captivity and the individual cases of abortions/embryo-fetal death did not show any consistent relationship to dosing or duration of dosing with tocilizumab. Although IL-6 does not seem to be a critical cytokine for either fetal growth or the immunological control of the maternal/fetal interface, a relation of this finding to tocilizumab cannot be excluded.

Transfer of a murine analogue of tocilizumab into the milk of lactating mice has been observed.

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

The non-clinical safety profile of tocilizumab in the cynomolgus monkey does not suggest a difference between IV and SC routes of administration.

4 PHARMACEUTICAL PARTICULARS

4.1 Storage

Intravenous tocilizumab:

This medicine should not be used after the expiry date (EXP) shown on the pack.

For vials: Store between 2ºC and 8ºC, do not freeze. Keep the container in the outer carton in order to protect from light.

For prepared infusion solution: The prepared infusion solution of tocilizumab is physically and chemically stable in 0.9% w/v sodium chloride solution. It can be stored for 24 hours at 30ºC and up to 2 weeks in a refrigerator at 2ºC - 8°C.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2ºC – 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

Subcutaneous tocilizumab:

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

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

4.2 Special Instructions for Use, Handling and Disposal

Intravenous tocilizumab:

Parenteral medications should be inspected visually for particulate matter or discoloration prior to administration.

Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles must be infused.

Use a sterile needle and syringe to prepare tocilizumab

Rheumatoid Arthritis and Coronavirus disease 2019 (COVID-19)

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

pJIA and sJIA Patients ≥ 30 kg:

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

pJIA Patients below 30 kg:

From a 50 ml infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.5 ml/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of tocilizumab under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

sJIA Patients below 30 kg:

From a 50 ml infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.6 ml/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of tocilizumab under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

Subcutaneous tocilizumab:

Do not use if the medicine is cloudy or contains particles, is any color besides colorless to yellowish, or any part of the PFS+NSD or pre-filled pen appears to be damaged.

Disposal of syringes/sharps

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

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

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

Disposal of Unused/Expired Medicines

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

4.3 Packs

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

Medicine: keep out of reach of children

Current at August 2022

Vials:

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

by Chugai Pharma Manufacturing Co., Ltd, Utsunomiya City, Japan

Pre-filled syringes:

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

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