▼This medicinal product is subject to additional monitoring in Australia due to provisional approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
Actemra® (tocilizumab)

1. NAME OF THE MEDICINE
Tocilizumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Actemra 80 mg/ 4 mL concentrate solution for intravenous infusion vial contains 80 mg tocilizumab

Actemra 200 mg/ 10 mL concentrate solution for intravenous infusion vial contains 200 mg tocilizumab

Actemra 400 mg/ 20 mL concentrate solution for intravenous infusion vial contains 400 mg tocilizumab

Actemra 162 mg/ 0.9 mL solution for subcutaneous (SC) injection contains 162 mg tocilizumab

Actemra SC 162 mg/ 0.9 mL solution for SC injection contains 162 mg tocilizumab.

Excipients with known effect
Actemra concentrated solution for intravenous infusion contains sodium.

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Concentrated solution for intravenous infusion
Actemra concentrated solution for intravenous (IV) infusion is a clear to opalescent, colourless to pale yellow sterile solution

Solution for subcutaneous injection
Actemra solution for subcutaneous (SC) injection is a clear to strongly opalescent, colourless to slightly yellowish sterile solution

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Rheumatoid Arthritis (IV and SC formulations)
Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs.

Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see section 5.1 Pharmacodynamic Properties, Clinical Trials) in combination with MTX in those not previously treated with MTX.

In the two groups of patients above, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.

Giant Cell Arteritis (SC formulations only)
Actemra is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

Coronavirus disease 2019 (COVID-19) (IV formulation only)
Actemra has **provisional approval** for the treatment of coronavirus disease 2019 (COVID-19) in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Provisional approval has been made on the basis of short-term efficacy and safety data. Continued approval depends on the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.

Polyarticular Juvenile Idiopathic Arthritis (IV and SC formulations)
Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate (MTX). Actemra can be given alone or in combination with MTX.

Systemic Juvenile Idiopathic Arthritis (IV and SC formulations)
Intravenous formulation
Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

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

Actemra IV and SC can be given alone or in combination with methotrexate (MTX).

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose
Treatment should be initiated by healthcare professionals experienced not only in the diagnosis and treatment of RA, GCA, pJIA, sJIA or CRS but also in the use of biological therapies for these conditions. For pJIA and sJIA treatment should be prescribed by medical practitioners experienced in the management of these conditions.

For adult patients with RA and children with pJIA and sJIA, Actemra may be administered as an IV infusion or a SC injection.

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

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

For paediatric and adult patients with CRS, Actemra is administered as an IV infusion.

Actemra IV formulation is not intended for SC administration.

Actemra SC formulation is not intended for IV administration.

For the treatment of patients with pJIA sJIA and CRS Actemra administration as an IV infusion should be administered in a hospital setting with immediate access to the necessary medical personnel and full resuscitation facilities (see section 4.4 Special Warnings and Precautions and section 4.8 Adverse Effects (Undesirable Effects)).

Subcutaneous Administration
Subcutaneous Actemra is indicated in the treatment of patients with adult RA, GCA, pJIA and sJIA.

For patients receiving Actemra as an SC injection, at least the first injection must be performed under the supervision of a qualified healthcare professional, in a healthcare facility with the necessary medical treatment available (including resuscitation equipment, protocols and appropriately trained personnel) in case of the need to initiate management of serious hypersensitivity reactions, including anaphylaxis. The patient must be closely monitored during the injection and afterwards for any signs and symptoms of a hypersensitivity reaction.

Patients transitioning from IV Actemra 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 healthcare professional.

Subcutaneous Actemra is intended for use under the guidance and supervision of the patient's treating physician. After proper training in injection technique, patients or parent/guardian may inject with Actemra only if their treating physician determines that it is appropriate and is satisfied that the patient or parent/guardian can safely inject in the home environment and with medical follow-up as necessary.

Assess suitability of patient or parent/guardian for SC home use and instruct patients or parent/guardian to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4 Special Warnings and Precautions for Use). Treating healthcare professionals must ensure that the patient or parent/guardian is aware of the signs of hypersensitivity and the risk of anaphylaxis, and is capable of seeking assistance should early features of a serious hypersensitivity reaction occur.

The pre-filled syringe with needle safety device can be used to treat paediatric patients of all approved ages. The pre-filled pen (ACTPen) should not be used to treat children and adolescent patients < 12 years of age.

<u>Rheumatoid Arthritis in Adults (IV or SC formulation)</u>

Intravenous Dosing Regimen
The recommended dose of Actemra for adult patients is 8 mg/kg given once every 4 weeks as an IV infusion.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see section 5.2 Pharmacokinetic Properties).

Actemra can be used alone or in combination with MTX and/or other non-biological DMARDs.

Actemra IV formulation should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (see below Method of Administration). The recommended duration of IV infusion is 1 hour.

During IV infusion, and for 30 minutes' post-infusion with Actemra, the patient must be closely monitored at all times for any signs or symptoms of a hypersensitivity reaction. Should any such reaction occur then appropriate urgent responses and treatments are to be initiated. The necessary equipment, treatments and protocols sufficient to initiate the management of acute anaphylaxis are to be in place along with the availability of appropriately trained personnel. There must be continued education and training of the health care professionals who administer the infusions. As part of the informed consent process patients should be made aware of the risk of anaphylaxis and the equipment, treatments and protocols in place to manage this risk.

Subcutaneous Dosing Regimen
The recommended dose of Actemra for adult patients is 162 mg given once every week as a subcutaneous injection.

Actemra can be used alone or in combination with MTX and/or other non-biological DMARDs.

At least the first injection must be performed under the supervision of a qualified healthcare professional, in a healthcare facility with the necessary medical treatment available (including resuscitation equipment, protocols and appropriately trained personnel) in case of the need to initiate management of serious hypersensitivity reactions, including anaphylaxis (see section 4.2 Dose and Method of Administration, Subcutaneous Administration for information about requirements for patients who may be suitable for SC home use).

<u>Dose Modification Recommendations for RA</u>

- Liver enzyme abnormalities

Lab Value	**Action**
> 1 to 3 x ULN	Dose modify concomitant DMARDs if appropriate For patients receiving intravenous Actemra with persistent increases in this range, reduce Actemra dose to 4 mg/kg or interrupt Actemra until ALT/AST have normalised. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate. For patients receiving subcutaneous Actemra with persistent increases in this range, reduce Actemra injection frequency to every other week or interrupt Actemra until ALT/AST have normalised. Restart with weekly injection or injection every other week, as clinically appropriate.

Lab Value	Action
> 3 to 5 x ULN	Interrupt Actemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN (confirmed by repeat testing, see section 4.4 Special Warnings and Precautions for Use), discontinue Actemra.
> 5 x ULN	Discontinue Actemra.

- Low absolute neutrophil count (ANC)

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

- Low platelet count

Lab Value (cells x 10^9/L)	Action
50 to 100	Interrupt Actemra dosing For patients receiving intravenous Actemra, when platelet count is > 100 x 10^9/L resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. For patients receiving subcutaneous Actemra, when platelet count is > 100 x 10^9/L resume Actemra injection every other week and increase frequency to every week, as clinically appropriate.
< 50	Discontinue Actemra.

Giant Cell Arteritis (SC formulation only)

The recommended dose of Actemra for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids. A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

Actemra can be used alone following discontinuation of glucocorticoids.

Data on use of Actemra beyond 52 weeks is limited. Treatment beyond 52 weeks should be guided by disease activity, physician assessments, patient choice and emerging data.

In the event of patients experiencing a relapse of GCA during the course of Actemra 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.

Actemra SC formulation is not intended for IV administration.

At least the first injection must be performed under the supervision of a qualified healthcare professional, in a healthcare facility with the necessary medical treatment available (including resuscitation equipment, protocols and appropriately trained personnel) in case of the need to initiate management of serious hypersensitivity reactions, including anaphylaxis. The patient must be closely monitored during the injection and afterwards for any signs and symptoms of a hypersensitivity reaction.

Subcutaneous Actemra is intended for use under the guidance and supervision of the patient's treating physician. After proper training in injection technique, patients may self-inject with Actemra only if their treating physician determines that it is appropriate and is satisfied that the patient can safely self-inject in the home environment and with medical follow-up as necessary.

Assess suitability of patient for SC home use and instruct patients to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4 Special Warnings and Precautions). Treating healthcare professionals must ensure that the patient is aware of the signs of hypersensitivity and the risk of anaphylaxis, and is capable of seeking assistance should early features of a serious hypersensitivity reaction occur.

Dose Modification Recommendations for GCA

- Liver enzyme abnormalities

Lab Value	**Action**
> 1 to 3 x ULN	Dose modify concomitant immunomodulatory agents if appropriate. For patients with persistent increases in this range, reduce Actemra injection frequency to every other week or interrupt Actemra until ALT/AST have normalised. Restart with weekly injection or injection every other week, as clinically appropriate.
> 3 to 5 x ULN	Interrupt Actemra dosing until < 3 x ULN and follow recommendations above for >1 to 3 x ULN. For persistent increases > 3 x ULN (confirmed by repeat testing, see section 4.4 Special Warnings and Precautions for Use), discontinue Actemra.
> 5 x ULN	Discontinue Actemra.

- Low absolute neutrophil count (ANC)

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

- Low platelet count

Lab Value (cells x 10^9/L)	Action
50 to 100	Interrupt Actemra dosing. When platelet count is > 100 x 10^9/L resume Actemra injection every other week and increase frequency to every week, as clinically appropriate.
< 50	Discontinue Actemra.

Missed dose (GCA/RA)
If a patient misses a weekly injection of Actemra within 7 days of the scheduled dose, they should be instructed to take the missed dose on the next scheduled day. If a patient misses a fortnightly (i.e. every other week) injection of Actemra within 7 days of the scheduled dose, they should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

Cytokine Release Syndrome (CRS) (adults and paediatrics)
The recommended dose for treatment of CRS is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg given as a 60-minute intravenous infusion.

Actemra can be given alone or in combination with corticosteroids.

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

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

COVID-19 (IV formulation only)
The recommended dose of Actemra for treatment of adult patients with COVID-19 is a single 60-minute infusion of 8 mg/kg.

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

Intravenous Dosing Regimen
The recommended dose of IV Actemra for patients with pJIA is:

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

given once every four weeks as an IV infusion.

The recommended duration of IV infusion is 1 hour.

Subcutaneous Dosing Regimen

The recommended dose of SC Actemra 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 pre-filled syringe with needle safety device can be used to treat paediatric patients of all approved ages. The pre-filled pen (ACTPen) should not be used to treat children and adolescent patients < 12 years of age.

At least the first injection must be performed under the supervision of a qualified healthcare professional, in a healthcare facility with the necessary medical treatment available (including resuscitation equipment, protocols and appropriately trained personnel) in case of the need to initiate management of serious hypersensitivity reactions, including anaphylaxis. (see section 4.2 Dose and Method of Administration, Subcutaneous Administration for information about requirements for patients who may be suitable for SC home use).

Missed dose (pJIA)

If a pJIA patient misses a subcutaneous injection of Actemra within 7 days of the scheduled dose, they should inject the missed dose as soon as they remember and give the next dose at the regular scheduled time. If a patient misses a subcutaneous injection of Actemra by more than 7 days of the scheduled dose or is unsure when to inject the next dose, they should contact their Healthcare professional.

Systemic Juvenile Idiopathic Arthritis (sJIA) (IV and SC formulations)
A change in dose should only be based on a consistent change in the patient's body weight over time. Actemra can be used alone or in combination with MTX.

Intravenous dosing regimen
The recommended dose of IV Actemra for patients with sJIA is:

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

given once every two weeks as an IV infusion.

The recommended duration of IV infusion is 1 hour.

Subcutaneous dosing regimen
The recommended dose of SC Actemra 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 must have a minimum body weight of 10 kg when receiving Actemra subcutaneously. The pre-filled syringe with needle safety device can be used to treat paediatric patients of all approved ages. The pre-filled pen (ACTPen) should not be used to treat children and adolescent patients < 12 years of age.

Missed dose (sJIA)

If a patient misses a weekly injection of Actemra within 7 days of the scheduled dose, they should be instructed to take the missed dose on the next scheduled day. If a patient misses a

fortnightly (i.e. every other week) injection of Actemra within 7 days of the scheduled dose, they should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

Dose Modification Recommendations for pJIA and sJIA:
Dose reduction of Actemra has not been studied in the pJIA or sJIA population. Dose interruptions of Actemra for laboratory abnormalities are recommended in patients with pJIA or sJIA at levels similar to what is outlined above for patients with RA (see section 4.4 Special Warnings and Precautions). If appropriate, concomitant MTX and/or other medications should be dose modified or stopped and Actemra dosing interrupted until the clinical situation has been evaluated. In pJIA or sJIA the decision to discontinue Actemra for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Special Populations

Children
The safety and efficacy of Actemra in children below 18 years of age with conditions other than pJIA, sJIA or CRS have not been established. The safety and efficacy in patients aged less than 2 years with pJIA and CRS have not been established. The safety and efficacy in patients aged less than 2 years with IV Actemra in sJIA or less than 1 year with SC Actemra in sJIA have not been established. Actemra subcutaneous formulation is not intended to be given to children with sJIA weighing less than 10 kg.

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

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment (see section 5.2 Pharmacokinetic Properties). Actemra has not been studied in patients with severe renal impairment.

Hepatic impairment
The safety and efficacy of Actemra has not been studied in patients with hepatic impairment (see section 4.4 Special Warnings and Precautions) and therefore no dose recommendations can be made.

Method of Administration

Concentrated solution for intravenous infusion
Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration.

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

Use a sterile needle and syringe to prepare Actemra IV formulations.

Rheumatoid Arthritis, CRS and COVID-19 patients (≥ 30 kg)
From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the Actemra solution required for the patient's dose, and discard. Withdraw the required amount of Actemra (0.4 mL per kg of the patient's body weight) under aseptic conditions and add to the infusion bag. To mix the solution, gently invert the bag to avoid foaming.

Use in paediatric patients

pJIA, sJIA and CRS patients ≥ 30 kg

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

pJIA patients below 30 kg

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

sJIA and CRS patients below 30 kg

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

Solution for Subcutaneous Injection

Actemra SC formulation is administered with a single-use pre-filled syringe or pen. The pre-filled pen (ACTPen) should not be used to treat children and adolescent patients < 12 years of age since there is a potential risk of intramuscular injection due to a thinner subcutaneous tissue layer.

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. Administration in the thigh may result in slightly increased absorption compared to the other recommended injection sites but this is not considered clinically relevant.

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

Actemra should not be shaken.

After removing the pre-filled syringe from the refrigerator, it should be allowed to reach room temperature by waiting for 25 to 30 minutes, before injecting. After removing the cap the injection should be started within 5 minutes.

After removing the pre-filled pen from the refrigerator, it should be allowed to reach room temperature by waiting 45 minutes, before injecting. After removing the cap the injection should be started within 3 minutes.

4.3 CONTRAINDICATIONS

Actemra is contraindicated in patients with:

- known hypersensitivity to any component of the product or with a history of any reaction consistent with hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies
- active, severe infections (see section 4.4 Special Warnings and Precautions)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve the traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded in the patient medical record. Substitution by any other biological medicinal product requires the consent of the prescribing physician.

All Indications

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra (see section 4.8 Adverse Effects (Undesirable Effects)). Actemra treatment should not be initiated in patients with active infections (see section 4.3 Contraindications). If a patient develops a serious infection, administration of Actemra should be interrupted until the infection is controlled. Physicians should exercise caution when considering the use of Actemra in patients with a history of recurring or chronic infection, or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections.

In patients with COVID-19, Actemra 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 Actemra, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reaction. The effects of Actemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which include younger children who may be less able to communicate their symptoms) and parents/guardians of minors should be instructed to contact a physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

The use of Actemra is not recommended in patients with HIV, positive core antibody for hepatitis B, prior HCV infection, or symptomatic EBV infection. Viral reactivation (e.g. hepatitis B) has been reported with biologic therapies for RA. In clinical studies with Actemra, patients who screened positive for hepatitis were excluded.

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

Gastrointestinal Perforation - Complications of Diverticulitis

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

Tuberculosis

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

Patients should be instructed to seek medical advice if signs or symptoms suggestive of a TB infection (e.g. persistent cough, wasting/weight loss, low grade fever) occur during or after therapy with Actemra.

Vaccinations

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

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

In a small, randomised open-label study, adult RA patients treated with Actemra plus MTX had a response to both the 23-valent pneumococcal polysaccharide (PPV) and tetanus toxoid (TTV) vaccines comparable to the response seen in patients receiving MTX only (60% vs 71% for PPV; 42% vs 39% for TTV, respectively). Because of the small number of patients in the study no firm conclusions can be drawn about the absolute differences in antibody responses between the two groups.

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

The efficacy and safety of Actemra for the treatment of COVID-19 has not been established in subjects who have received a COVID-19 vaccine at any time prior to its administration

Hypersensitivity Reactions, including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with Actemra (see section 4.8 Adverse Effects (Undesirable Effects)) and anaphylactic events with a fatal outcome have been reported with intravenous infusions of Actemra. In the post-marketing setting, events of serious hypersensitivity and anaphylaxis, have occurred in patients treated with a range of doses of Actemra, including intravenous and subcutaneous administration of Actemra, with or without concomitant therapies, premedication and/or a previous hypersensitivity reaction.

In the post marketing setting, cases with a fatal outcome have been reported with intravenous Actemra. These events have occurred as early as the first infusion of Actemra (see section 4.3 Contraindications and section 4.8 Adverse Effects (Undesirable Effects)). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with Actemra.

The treating healthcare professional should consider the risks of potential hypersensitivity reactions when assessing a patient's suitability for home use with subcutaneous Actemra. Healthcare professionals should ensure training in the subcutaneous injection technique is

provided to patients. Serious hypersensitivity reactions have occurred with subcutaneous Actemra and anaphylaxis has occurred in the post-marketing setting. Hypersensitivity reactions, including anaphylaxis, may occur even after multiple injections of subcutaneous Actemra. Inform patients that some patients who have been treated with Actemra have developed serious allergic reactions, including anaphylaxis. Instruct patients to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.2 Dose and Method of Administration).

If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately and Actemra should be permanently discontinued.

Patients with a history of any reaction consistent with hypersensitivity (e.g. urticaria, bronchospasm, angioedema) to Actemra or any component of the product must not be re-challenged with Actemra (see section 4.3 Contraindications).

Viral Reactivation

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

Active Hepatic Disease and Hepatic Impairment

Treatment with Actemra particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases therefore caution should be exercised. Treatment with Actemra is not recommended in patients with active hepatic disease or hepatic impairment (see section 4.8 Adverse Effects (Undesirable Effects) and section 4.2 Dose and Method of Administration).

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

Hepatotoxicity

Mild and moderate elevations of hepatic transaminases and bilirubin have been reported with Actemra treatment (see section 4.8 Adverse Effects (Undesirable Effects)). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with Actemra. There is a potential risk of hepatotoxicity with use of Actemra.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with Actemra (see section 4.8 Adverse Effects (Undesirable Effects), Post Marketing Experience). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of Actemra. Some of these cases have resulted in liver transplant or death. While most cases presented with marked elevations of transaminases (> 5 times ULN), some cases presented with signs or symptoms of liver dysfunction and only mildly elevated transaminases.

It is not recommended to initiate Actemra treatment in patients with elevated transaminases ALT or AST greater than 1.5 x ULN, except in cases of CRS (see section 4.2 Dose and Method of Administration). In RA, GCA, pJIA and sJIA patients who develop elevated ALT or AST greater than 5 x ULN, discontinue Actemra.

In RA and GCA patients, the ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications including Actemra discontinuation based on transaminases levels, see section 4.2 Dose and

Method of Administration. For ALT or AST elevations > 3 to 5 x ULN, confirmed by repeat testing, Actemra treatment should be interrupted. Once the patient's hepatic transaminases are below 3 x ULN, treatment with Actemra may recommence at 4 or 8 mg/kg for the IV formulation or every other week or weekly injection for the SC formulation.

In pJIA and sJIA patients, ALT and AST should be monitored at the time of the second administration and thereafter every 4 to 8 weeks for pJIA and every 2 to 4 weeks for sJIA (see section 4.2 Dose and Method of Administration).

Patients hospitalised with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognised as a complication of severe COVID-19. The decision to administer Actemra should balance the potential benefit against the risks of acute treatment with Actemra. In COVID-19 patients with elevated ALT or AST above 10 x ULN, administration of Actemra treatment is not recommended.

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

Haematological Abnormalities

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

In patients not previously treated with Actemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L. In RA, GCA, pJIA and sJIA patients with an ANC below 0.5 x 10^9/L, treatment is not recommended (see section 4.2 Dose and Method of Administration). In COVID-19 patients with an ANC below 1 x 10^9, administration of Actemra is not recommended.

Caution should be exercised when considering initiation of Actemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^9/L). In all patients, including COVID-19, with a platelet count < 50 x 10^9/L Actemra is not recommended (see section 4.2 Dose and Method of Administration).

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

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

In pJIA and sJIA patients, neutrophils and platelets should be monitored at the time of the second administration and thereafter every 4 to 8 weeks for pJIA and every 2 to 4 weeks for sJIA (see section 4.2 Dose and Method of Administration).

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

Lipid Parameters

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with Actemra (see section 4.8 Adverse Effects (Undesirable Effects)). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

Assessment of lipid parameters should be performed in patients 4 to 8 weeks following initiation of Actemra therapy. RA and sJIA patients should then be managed according to local clinical guidelines for management of hyperlipidaemia. For pJIA patients, assessment of lipid parameters should be performed at 3 monthly intervals during Actemra treatment until it is clear the risk of development of significant changes in lipid parameters has diminished.

Demyelinating Disorders

Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with Actemra is currently unknown. Multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies.

Malignancy

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

Patients receiving immunosuppressive therapy are at an increased risk of developing skin cancer (melanoma and non-melanoma). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer and exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Intravenous Infusion Reactions

Infusion reactions have been observed during and within 24 hours of treatment with Actemra (see section 4.8 Adverse Effects (Undesirable Effects)).

Cardiovascular Risk

RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care (see section 4.4 Special Warnings and Precautions for Use- Lipid Parameters). Elevations in LDL and HDL lipids have been observed, with no clinical consequences identified. No data are available concerning cardiovascular outcomes with long-term use of Actemra.

Combination with TNF Antagonists and/or other Biological Therapies

There is no experience with the use of Actemra with TNF antagonists or other biological treatments for RA. Actemra is not recommended for use with other biological agents including TNF antagonists, anakinra, rituximab and abatacept.

Sodium

Intravenous Actemra contains 1.17 mmol (26.55 mg) of sodium per maximum dose of 1200 mg. This should be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of Actemra contain less than 1 mmol of sodium (23 mg) and can essentially be considered ‘sodium free’.

The subcutaneous Actemra formulation does not contain sodium.

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, Actemra has not been studied in patients during an episode of active MAS (see section 4.8 Adverse Effects (Undesirable Effects)).

Use in the Elderly

Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of Actemra in adult RA patients. Results of these analyses showed that no adjustment of the dose is necessary for age, gender, or race.

No dose adjustment is required in elderly patients.

Paediatric use

The safety and efficacy of intravenous Actemra in children below 18 years of age with conditions other than pJIA, sJIA or CRS have not been established. Ten patients who participated in the pivotal study for pJIA were less than 4 years of age. The use of Actemra IV in children under the age of two have not been studied.

Available data only support use of intravenous Actemra in children with pJIA who have had an inadequate response to or intolerance to MTX. Long-term safety data for intravenous Actemra use in children with pJIA are currently limited to 2 years, and at present no comparison with the safety profile of other biological DMARDs approved for use in this indication has been made.

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 safety and efficacy of subcutaneous Actemra in children from birth to less than 1 year has not been established. No data are available. Data in patients with sJIA aged 1 year is limited (see section 5.2 Pharmacokinetic Properties). Three patients aged 1-2 were included in Study WA28118. The safety and efficacy of Actemra SC has not been established for patients with CRS or children below 2 years of age with pJIA. The pre-filled pen (ACTPen) should not be used to treat children and adolescent patients < 12 years of age since there is a potential risk of intramuscular injection due to a thinner subcutaneous tissue layer.

Effects on laboratory tests

Caution should be exercised when considering initiation of Actemra treatment in patients with a low neutrophil count. Decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4%, with counts < 0.5 x 10^9/L occurring in 0.3%, of patients on Actemra 8 mg/kg + DMARD without clear association with serious infection (see section 4.4 Special Warnings and Precautions and 4.8 Adverse Effects (Undesirable Effects)). In patients with an absolute neutrophil count < 0.5 x 10^9/L treatment is not recommended.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

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

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

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

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP3A4 and to a lesser extent CYP1A2, CYP2C9 and CYP2C19 enzyme messenger RNA (mRNA) expression. Actemra was shown to normalise expression of the mRNA for these enzymes.

This 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 and its acid metabolite (CYP3A4 substrates) were decreased by 57% and 39%, respectively, one week following a single dose of Actemra, to a level similar or slightly higher than those observed (in other studies) in healthy subjects.

When starting or stopping therapy with Actemra, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin or benzodiazepines) should be monitored as doses may need to be adjusted to maintain therapeutic effect. The degree of dose up-titration upon initiation of therapy or dose down-titration when stopping therapy with Actemra should be based on the therapeutic response and/or adverse effects of the patient to the individual medicine. Given a relatively long elimination half-life (t1/2), the effect of Actemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

Use in Pregnancy - Category C

Actemra should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of Actemra in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with Actemra.

In an embryo-foetal toxicity study conducted in cynomolgus monkeys, a slight increase of abortion/embryo-foetal death was observed with high systemic cumulative exposure in the 10 mg/kg/day mid-dose group (> 35 times human exposure) and in the 50 mg/kg/day high-dose group (> 100 times human exposure) compared to vehicle control and low-dose groups. It cannot be excluded that this finding is related to Actemra treatment. Placental transfer of both Actemra and anti-Actemra antibodies to the foetus was seen in cynomolgus monkeys.

Use in Lactation

It is unknown whether Actemra is excreted in human breast milk and its efficacy and safety in lactating women has not been established. However, it is known that endogenous immunoglobulins of the IgG isotype are excreted into human milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Actemra should be made taking into account the benefit of breast-feeding to the child and the benefit of Actemra therapy to the woman.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed and there is no evidence from the available data that Actemra treatment affects the ability to drive and use machines. However, given that dizziness has been reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Rheumatoid Arthritis

Patients Treated with Intravenous Actemra

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

The all control population includes all patients who received at least one dose of Actemra in the double-blind controlled period of the 5 studies. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind controlled studies 774 patients received Actemra 4 mg/kg in combination with MTX, 1870 patients received Actemra 8 mg/kg in combination with MTX/other DMARDs and 288 patients received Actemra 8 mg/kg monotherapy.

The all exposure population includes all patients who received at least one dose of Actemra either in the double-blind control period or open label extension phase in studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years. The mean duration of exposure to Actemra in the all exposure population was 2.14 years.

The most commonly reported AEs in controlled studies up to 2 years (occurring in ≥ 5% of patients treated with Actemra monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT and bronchitis. In study II the rate of AEs (including deaths, serious AEs and AEs leading to treatment withdrawal or dose modification) after 2 years, calculated as a function of exposure (i.e. events per 100 patient years), had not increased in comparison with the AE profile observed after 1 year of study II.

Table 1 Adverse Events occurring in at least 2% or more of patients on 8 mg/kg Actemra + DMARD and at least 1% greater than that observed in patients on placebo + DMARD

All Control Study Population					
Preferred Term	**Actemra 8 mg/kg monotherapy n=288 (%)**	**MTX n=284 (%)**	**Actemra 4 mg/kg + MTX n=774 (%)**	**Actemra 8 mg/kg + DMARDs n=1870 (%)**	**Placebo + DMARDs n=1555 (%)**
Upper Respiratory Tract Infection	7	5	9	9	7
Nasopharyngitis	7	6	5	7	5
Headache	7	2	6	6	4
Hypertension	6	2	6	5	3
Cough	3	0	3	3	2
ALT increased	6	4	3	3	1
Diarrhoea	5	5	5	4	4
Back Pain	2	1	3	4	3
Peripheral Oedema	2	0	2	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	2	2	1
Transaminase increased	1	5	3	3	1

Other infrequent and medically relevant adverse events occurring at an incidence of less than 2% in RA patients treated with Actemra in controlled trials were:

Infections and infestations: cellulitis, oral herpes simplex, herpes zoster, diverticulitis
Gastrointestinal disorders: stomatitis, gastric ulcer
Skin and subcutaneous tissue disorders: pruritus, urticaria
Investigations: weight increased, total bilirubin increased
Blood and lymphatic system disorders: leucopenia, neutropenia
Metabolism and nutrition disorders: hypercholesterolaemia, hypertriglyceridaemia
General disorders and administration site conditions: hypersensitivity reaction
Respiratory, thoracic and mediastinal disorders: dyspnoea
Eye disorders: conjunctivitis
Renal disorders: nephrolithiasis
Endocrine disorders: hypothyroidism

Infections

In the 6 month controlled clinical trials, the rate of all infections reported with Actemra 8 mg/kg + DMARD treatment was 127 events per 100 patient (pt) years compared to 112 events per 100 pt years in the placebo + DMARD group. In the *all exposure* population the overall rate of infections with Actemra 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 Actemra 8 mg/kg + DMARD was 5.3 events per 100 pt years exposure compared to 3.9 events per 100 pt years exposure in the placebo + DMARD group. In the monotherapy

study the rate of serious infections was 3.6 events per 100 pt years of exposure in the Actemra group and 1.5 events per 100 pt years of exposure in the MTX group.

In the 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 active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have also been reported.

Gastrointestinal Perforation

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

Infusion Reactions

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

The rate of anaphylactic reactions (occurring in a total of 8/4009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose.

Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation, were reported in a total of 56 out of 4009 patients (1.4%) treated with Actemra during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of Actemra.

Immunogenicity

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

Early Rheumatoid Arthritis

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

The overall rate of serious adverse events (SAEs) per 100 patient years (PY) was numerically higher for the Actemra arms (13.2 SAEs per 100 PY) than the placebo + MTX arm (10.6 SAEs per 100 PY). These were reported under ‘Infections and Infestations’, ‘Neoplasms Benign, Malignant and Unspecified’, ‘Respiratory, Thoracic and Mediastinal Disorders’ and ‘Injury, Poisoning and Procedural Complications’.

The rate of discontinuation due to an adverse event was approximately twice as high in the Actemra arms, as in the placebo + MTX arm (16.1 and 8.2 events per 100 PY respectively). In all 3 Actemra treatment arms, the most common reason for treatment discontinuation was attributed to 'Investigations' events, in particular events related to liver enzyme elevations. In the study there were 14 patient deaths reported, 12 in Actemra-treated patients and 2 in Placebo + MTX-treated patients.

Actemra vs adalimumab in monotherapy

In a 24-week double-blinded, parallel study (monotherapy with Actemra 8 mg/kg IV q4w (n=162) compared to adalimumab 40 mg SC q2w (n=162)), the overall clinical adverse event profile was similar between Actemra and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (Actemra 11.7% vs. adalimumab 9.9%) with the most common event being infections (3.1% each). There was a sudden death in the Actemra arm of a patient who died 10 days after the last dose. The cause of death was unknown. The patient had a history of peripheral vascular disease, hypertension, smoking and interstitial lung disease. Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with Actemra compared with adalimumab. Four (2.5%) patients in the Actemra arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the Actemra arm and 5 (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. For patients not receiving lipid lowering agents the mean increase in LDL from baseline to week 24 was 0.64 mmol/L (25 mg/dL) for patients in the Actemra arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the Actemra arm was consistent with the known safety profile of Actemra and no new or unexpected adverse drug reactions were observed.

Patients Treated with Subcutaneous Actemra

The safety of subcutaneous Actemra includes data from Study VI (SUMMACTA) and Study VII (BREVACTA). SUMMACTA compared the efficacy and safety of subcutaneous Actemra 162 mg administered every week versus intravenous Actemra 8 mg/kg every 4 weeks in 1262 subjects with adult RA. BREVACTA was a placebo-controlled superiority study that evaluated the safety and efficacy of subcutaneous Actemra 162 mg administered every other week or placebo in 656 patients. All patients in both studies received background non-biological DMARD(s).

The safety and immunogenicity observed for subcutaneous Actemra was consistent with the known safety profile of intravenous Actemra and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions was observed in patients who received subcutaneous Actemra compared with those who received subcutaneous placebo injections (in the IV arms of the studies).

<u>Injection Site Reactions</u>

During the 6-month controlled period in SUMMACTA, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the subcutaneous Actemra and the subcutaneous placebo (in the IV arm of the study) weekly injections, respectively. In BREVACTA, the frequency of injection site reactions was 7.1% (31/437) and 4.1% (9/218) for the subcutaneous Actemra and placebo every other week, respectively. These injection site reactions (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority was resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity
In SUMMACTA, a total of 625 patients treated with Actemra 162 mg weekly were tested for anti-Actemra antibodies in the 6 month controlled period. Five patients (0.8%) developed positive anti-Actemra antibodies; of these, all developed neutralising anti-Actemra antibodies. In BREVACTA, a total of 434 patients treated with Actemra 162 mg every other week were tested for anti-Actemra antibodies. Seven patients (1.6%) in the subcutaneous Actemra arm developed anti-Actemra antibodies; of these 6 (1.4%) in the subcutaneous Actemra arm developed neutralising antibodies.

A total of 1454 subcutaneous Actemra all exposure patients have been tested for anti-Actemra antibodies, 13 patients (0.9%) developed positive anti-Actemra antibodies, and of these 12 patients (0.8%) developed neutralising anti-Actemra antibodies.

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

Hypersensitivity and Anaphylaxis
In the subcutaneous Actemra development program clinically significant hypersensitivity reactions were defined as any adverse event during or within 24 hours of an injection (excluding injection site reactions), related to treatment and leading to study withdrawal. Clinically significant hypersensitivity reactions were experienced in 0.7% (8 out of 1068) of patients in the subcutaneous 6-month controlled RA trials and 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population. The events included, but were not limited to hypersensitivity (5 events) and urticaria (1 event).

There were no cases of anaphylaxis in the subcutaneous Actemra pivotal studies SUMMACTA and BREVACTA, however anaphylaxis has been reported in the post-market setting.

Giant Cell Arteritis
The safety of subcutaneous Actemra was studied in 251 GCA patients in a Phase III study (Study X, GiACTA). The total patient years duration in the Actemra 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 Actemra treatment groups was consistent with the known safety profile of Actemra (see Table 1).

Infections
The rate of infection/serious infection events was 200.2/9.7 events per 100 patient years in the Actemra weekly group and 160.2/4.4 events per 100 patient years in the Actemra every other week group compared to 156.0/4.2 events per 100 patient years in the placebo plus 26 week prednisone taper 210.2/12.5 events per 100 patient years in the placebo plus 52 weeks taper groups.

Injection Site Reactions
In the Actemra weekly group and the every other week group, 6% (6/100) of patients and 14% (7/49) of patients, reported an adverse reaction occurring at the site of a subcutaneous injection, respectively. No injection site reaction was reported as a serious adverse event or required treatment discontinuation.

Immunogenicity
In the Actemra weekly group and the every other week group, 1 patient (1.1%, 1/95) and 3 patients (6.5%, 3/46), developed positive neutralising anti-Actemra antibodies, respectively. These were not of the IgE isotype. These patients did not develop hypersensitivity reactions or injection site reactions.

Hypersensitivity and Anaphylaxis
In the Actemra weekly group, no patients experienced a clinically significant hypersensitivity reaction or anaphylaxis. Two patients in the Actemra every other week group had clinically significant hypersensitivity reactions. One patient in the Actemra every other week group experienced events constituting an anaphylactic reaction. These were not considered to be clinically significant upon medical review.

COVID-19
The safety evaluation of Actemra in COVID-19 was based on 3 randomised, double-blind, placebo controlled trials (studies EMPACTA, COVACTA and REMDACTA). A total of 974 patients were exposed to Actemra in these studies. Safety data from the randomised, controlled, open-label, platform trial (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 Actemra treated patients and more commonly than in patients on placebo in the pooled safety-evaluable population from clinical studies EMPACTA, COVACTA and REMDACTA.

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 Actemra[2]

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 EMPACTA, COVACTA and REMDACTA

Description of selected adverse drug reactions from clinical trials

Infections
In the pooled safety-evaluable population from the studies EMPACTA, COVACTA and REMDACTA, the rates of infection/serious infection events were balanced between COVID-19 patients receiving Actemra (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 Actemra 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 Actemra and in 30.5% and 22.9% of patients treated with placebo, respectively.

Figure 1 – Meta-Analysis Pooled Safety Population – Summary of adverse events of special interest.

	PBO (N=483)	TCZ 8 mg/kg (N=974)	All Patients (N=1457)
Total number of patients with at least one AESI	189 (39.1%)	387 (39.7%)	576 (39.5%)
Total number of AESIs	370	686	1056
Total number of patients with at least one			
Serious Infection	110 (22.8%)	181 (18.6%)	291 (20.0%)
Infections	155 (32.1%)	295 (30.3%)	450 (30.9%)
Opportunistic infections	8 (1.7%)	7 (0.7%)	15 (1.0%)
Malignancies	0	2 (0.2%)	2 (0.1%)
Medically Confirmed Malignancies	0	1 (0.1%)	1 (<0.1%)
Hepatic events	6 (1.2%)	17 (1.7%)	23 (1.6%)
Stroke	16 (3.3%)	19 (2.0%)	35 (2.4%)
Myocardial infarction	3 (0.6%)	7 (0.7%)	10 (0.7%)
Hypersensitivity Adverse Events	13 (2.7%)	39 (4.0%)	52 (3.6%)
Anaphylactic reaction events according to Sampson's Criteria	1 (0.2%)	3 (0.3%)	4 (0.3%)
Anaphylactic reaction events	0	2 (0.2%)	2 (0.1%)
Gastrointestinal perforations	3 (0.6%)	5 (0.5%)	8 (0.5%)
Medically Confirmed Gastrointestinal perforations	1 (0.2%)	1 (0.1%)	2 (0.1%)
Bleeding events	50 (10.4%)	120 (12.3%)	170 (11.7%)
Serious Bleeding	15 (3.1%)	28 (2.9%)	43 (3.0%)
Demyelinating events	0	0	0

Polyarticular Juvenile Idiopathic Arthritis
The safety profile of Actemra was studied in 240 paediatric patients with pJIA. In the CHERISH study, 188 patients (2 to 17 years of age) were treated with IV Actemra and in the JIGSAW study, 52 patients (1 to 17 years of age) were treated with SC Actemra. The total patient exposure to Actemra in the pJIA all exposure population was 184.4 patient years for IV Actemra and 50.4 patient years for SC Actemra. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of Actemra with the exception of injection site reactions (see Table 1). A higher frequency of injection site reactions was experienced by pJIA patients following SC Actemra injections compared to adult RA patients (see 4.8 Adverse effects (Undesirable effects)).

Infections
Infections are the most commonly observed events in pJIA. The rate of infections in the pJIA IV Actemra all exposure population was 163.7 per 100 pt years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was 4.9 per 100 pt years. The rate of serious infections was numerically higher in patients weighing below 30 kg treated with 10 mg/kg Actemra (12.2 per 100 pt years) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg Actemra (4.0 per 100 pt years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing below 30 kg treated with 10 mg/kg Actemra (21%) compared to patients weighing ≥

30 kg, treated with 8 mg/kg Actemra (8%). The rate of infection in pJIA patients treated with SC Actemra was comparable with pJIA patients treated with IV Actemra.

Infusion Reactions

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

No clinically significant hypersensitivity reactions were reported.

Injection Site Reactions

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

Immunogenicity

Across the two studies in pJIA patients, only four patients developed neutralising anti-Actemra (Nab) antibodies. Of the four patients (0.5% [1/188] in the IV Study WA19977 and 5.8% [3/52] in the SC Study WA28117) that developed positive neutralising anti-Actemra antibodies, none developed a serious or clinically significant hypersensitivity reaction. Of these 4 patients, 2 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed.

Systemic Juvenile Idiopathic Arthritis

The safety profile of Actemra in sJIA was studied in 163 paediatric patients. In Study WA18221 (12-week trial and long term extension), 112 patients (2 to 17 years of age) were treated with IV Actemra and in Study WA28118 (52-week trial), 51 patients (1 to 17 years of age) were treated with SC Actemra.

In general, the ADRs in patients with sJIA were similar in type to those seen in RA and pJIA patients (see section 4.8 Adverse Effects (Undesirable Effects)).

Infections

In the 12 week controlled trial (Study WA18221) the rate of all infections in the IV Actemra group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the on-going open label extension study (Part II) the overall rate of infections remained similar at 306.6 per 100 patient years.

In the 12 week controlled trial (Study WA18221) the rate of serious infections in the IV Actemra group was 11.5 per 100 patient years. In the open label extension study the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

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

In Australia, a case of fatal sepsis occurred in a 6-year old who had been treated with Actmera for approximately 2 years for sJIA. Methotrexate was given concomitantly. The patient had symptoms of gastroenteritis on the day preceding his death, and the last dose of Actemra was administered 10 days prior to the event. The death was assessed as related to septicemia.

Macrophage Activation Syndrome

In the 12 week controlled study (Study WA18221), no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment. Three per 112 (3%) developed MAS during open-label treatment with IV Actemra. One patient in the placebo group escaped to IV Actemra 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had Actemra dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the Actemra sJIA clinical development experience, however no definitive conclusions can be made.

A case of MAS with a fatal outcome was reported in a patient enrolled in a clinical study of Actemra in sJIA. The patient had interrupted Actemra treatment 4 weeks prior to the onset of MAS because of a rotavirus infection. The patient also experienced a worsening of sJIA prior to the diagnosis of MAS.

Infusion Reactions

For sJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion with IV Actemra. In the 12 week controlled trial (Study WA18221), 4.0% of patients from the Actemra group experienced events occurring during infusion, one event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

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

Clinically significant hypersensitivity reactions associated with IV Actemra and requiring treatment discontinuation were reported in 1 out of 112 patients (< 1%) treated with IV Actemra during the controlled and open-label parts of the clinical trial. In an open-label, single arm study over 12 weeks in paediatric sJIA patients (N=11) under 2 years of age, the safety and immunogenicity of Actemra was assessed descriptively. SAEs, AEs leading to discontinuation, and infectious AEs were reported by 27.3%, 36.4%, and 81.8% of patients. Six patients (54.5%) experienced hypersensitivity reactions, defined as all adverse events occurring during or within 24 hours after an infusion considered related to Actemra. Three of these patients experienced serious hypersensitivity reactions and were withdrawn from the study. Three patients with hypersensitivity reactions (two with serious hypersensitivity reactions) developed treatment induced anti-Actemra antibodies after the event. There were no cases of MAS based on the protocol-specified criteria, but 2 cases of suspected MAS based on Ravelli criteria. Reports of anaphylaxis, anaphylactoid reactions, and hypersensitivity reactions in patients under 18 years of age have been reported in the post-marketing setting.

Injection Site Reactions (ISRs)
In the Study WA28118, a total of 41.2% (21/51) sJIA patients experienced ISRs to SC Actemra. 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-Actemra antibodies at baseline. Two patients developed positive anti-Actemra 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-Actemra antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-Actemra antibodies post baseline.

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

Laboratory Abnormalities
Haematology abnormalities
Rheumatoid Arthritis
Neutrophils – Intravenous Administration
In the 6 month controlled trials decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on Actemra 8 mg/kg + DMARD compared to < 0.1% of patients on placebo + DMARD. Approximately half of the patients who developed an ANC < 1 x 10^9/L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving Actemra 8 mg/kg + DMARD (section 4.4 Special Warnings and Precautions).

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

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

Neutrophils - Subcutaneous Administration
During routine laboratory monitoring in the Actemra 6-month controlled period of SUMMACTA and BREVACTA, a decrease in neutrophil count below 1 × 10^9/L occurred in 2.9% and 2.3% of patients on Actemra 162 mg SC weekly and every other week, respectively.

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

Platelets – Intravenous Administration
In the 6 month controlled trials, decreases in platelet counts below 100 x 10^9/L occurred in 1.7% of patients on Actemra 8 mg/kg + DMARDs compared to < 1% on placebo + DMARDs. These decreases occurred without associated bleeding events. (see section 4.2 Dose and Method of Administration and section 4.4 Special 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.

Platelets - Subcutaneous Administration
During routine laboratory monitoring in the 6-month controlled period of SUMMACTA and BREVACTA, 1.6% and 1.4% of patients experienced a decrease in platelet count to < 100 × 10^9/L on Actemra 162 mg SC weekly and every other week, respectively.

Giant Cell Arteritis
Neutrophils
During routine laboratory monitoring in the Actemra 12-month double blind, placebo-controlled phase of Study X (GiACTA), a decrease in neutrophil count below 1 x 10^9/L occurred in 4% of patients in the Actemra weekly group. This was not observed in either of the placebo plus prednisone taper groups. There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Platelets
During routine laboratory monitoring in the Actemra 12-month double blind, placebo-controlled phase of Study X (GiACTA), one patient (1%, 1/100) in the Actemra weekly group had a single transient occurrence of decreased platelet count below 100 x 10^9/L without associated bleeding events. A decrease in platelet count below 100 x 10^9/L was not observed in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis
Neutrophils
During routine laboratory monitoring in the Actemra all exposure population, a decrease in neutrophil count below 1 × 10^9/L occurred in 3.7% of patients. There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Platelets
During routine laboratory monitoring in the Actemra all exposure population, a decrease in platelet count to ≤ 50 × 10^3/μL occurred in 1% of patients treated with IV Actemra without associated bleeding events and in no patients treated with SC Actemra.

Systemic Juvenile Idiopathic Arthritis
Neutrophils
During routine laboratory monitoring in the 12 week controlled trial (Study WA18221), a decrease in neutrophil counts below 1 × 10^9/L occurred in 7% of patients in the Actemra group, and in none in the placebo group. In the open-label extension study (WA18221) decreases in neutrophil counts below 1 x 10^9/L occurred in 15% of patients in the IV Actemra group.

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

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

Platelets
During routine laboratory monitoring in the 12 week controlled trial (Study WA18221), 3% of patients in the placebo group and 1% in the IV Actemra group had a decrease in platelet count to ≤ 100 × 10^3/μL. In the open-label extension study (WA18221) decreases in platelet counts

below 100 x $10^3/\mu L$ occurred in 3% of patients in the IV Actemra 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 Actemra.

Liver enzyme elevations

Rheumatoid Arthritis

Intravenous Administration

During the 6 month controlled trials transient elevations in ALT (alanine transaminase)/AST (aspartate transaminase) > 3 x ULN (Upper Limit of Normal) were observed in 2.1% of patients on Actemra 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received Actemra 8 mg/kg + DMARD compared to 1.5% of patients on placebo + DMARD. The addition of potentially hepatotoxic drugs (for example MTX) to Actemra monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5x ULN were observed in 0.7% of Actemra monotherapy patients and 1.4% of Actemra + DMARD patients, the majority of whom were discontinued from Actemra treatment. During routine laboratory monitoring, the incidence of indirect bilirubin > ULN is 6.2% in patients treated with 8 mg/kg Actemra + 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 VIII (FUNCTION), MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months) experienced more transient elevations in ALT > 3 x ULN compared with the all control population. Transient elevations in ALT > 3 to 5 x ULN were observed in 6.6% of patients on Actemra 4 mg/kg + MTX, 9.7% of patients on Actemra 8mg/kg + MTX compared to 3.4% of patients on Actemra 8 mg/kg + placebo and 3.9% of patients on MTX + placebo.

In Study WA25204 (ENTRACTE), of the 1538 patients with moderate to severe RA (see Section 5.1 Clinical trials) and treated with Actemra, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug induced hepatitis with hyperbilirubinemia was reported in association with Actemra treatment (see section 4.4 Special warnings and precautions for use).

Subcutaneous Administration

During routine laboratory monitoring in the Actemra 6-month controlled period of SUMMACTA, elevation in ALT or AST ≥ 3 x ULN occurred in 6.5% and 1.4% of patients, respectively on the SC weekly dose. In the 6-month controlled period of BREVACTA, elevation in ALT or AST ≥ 3 x ULN occurred in 3.4% and 0.7% of patients, respectively on the SC every other week dose.

Giant Cell Arteritis

During routine laboratory monitoring in the Actemra 12-month double blind, placebo-controlled phase of Study X (GiACTA), elevation in ALT ≥ 3 x ULN occurred in 3% of patients in the Actemra 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 x ULN occurred in 1% of patients in the Actemra weekly group, compared to no patients in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis

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

Systemic Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the 12 week controlled trial (Study WA18221), elevation in ALT or AST ≥ 3 x ULN occurred in 5% and 3% of patients, respectively, in the IV Actemra group, and in 0% of placebo patients.

In the open-label extension study (WA28118), elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients, respectively, in the IV Actemra 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 Actemra, respectively.

Elevations in lipid parameters

Rheumatoid Arthritis
Intravenous Administration
During routine laboratory monitoring in the 6 month controlled clinical trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. Approximately 24% of patients receiving Actemra in clinical trials experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL). Elevations in lipid parameters 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 6-month controlled periods of SUMMACTA and BREVACTA, 19% of patients on the SC weekly dose and 20% of patients dosed every other week experienced sustained elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 9% and 10% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) on the SC weekly dose and every other week dose.

Giant Cell Arteritis
During routine laboratory monitoring in the Actemra 12-month double blind, placebo-controlled phase of Study X (GiACTA), 25% of patients experienced elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 47% experiencing an increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the Actemra weekly group.

Polyarticular Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the IV Actemra Study, 3.4 % and 10.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 3.4 mmol/L (130 mg/dL) and total cholesterol value to ≥ 5.2 mmol/L (200 mg/dL) at any time during the study treatment, respectively. Of 185 patients assessed 19 patients experienced consecutive sustained elevation of their total cholesterol value ≥ 4.4 mmol/L (170 mg/dL) at any time during study treatment.

In the SC Actemra study, 14.3% and 12.8% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 3.4 mmol/L (130 mg/dL) and total cholesterol value to ≥ 5.2 mmol/L (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 ≥ 3.4 mmol/L (130 mg/dL) and total cholesterol value to ≥ 5.2 mmol/L (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 ≥ 3.4 mmol/L (130 mg/dL) and total cholesterol value to ≥ 5.2 mmol/L (200 mg/dL), respectively. Of 107 patients assessed 22 experienced consecutive sustained elevation of their total cholesterol value ≥ 4.4 mmol/L (170 mg/dL) at any time during study treatment.

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 ≥ 3.4 mmol/L (130 mg/dL) and total cholesterol value to ≥ 5.2 mmol/L (200 mg/dL), respectively.

Laboratory abnormalities-COVID-19 (IV administration)
The incidence of laboratory abnormalities was generally similar between patients with COVID-19 who received one or two doses of Actemra compared with those who received placebo in studies EMPACTA, COVACTA and REMDACTA with few exceptions. Decreases in platelets and neutrophils and elevations of ALT and AST were more frequent among patients receiving Actemra versus placebo.

Malignancies
The clinical data are insufficient to assess the potential incidence of malignancy following exposure to Actemra. Long-term safety evaluations are ongoing. Neoplasms Benign, Malignant, and Unspecified (including Cysts and Polyps): Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with Actemra.

Post-Marketing Experience
The following adverse drug reactions have been identified from clinical trials and/ or post marketing experience with Actemra (Table 3) 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)	**Frequency Category**
Immune system disorders	
Anaphylaxis (fatal)[1, 2]	Rare
Skin and subcutaneous tissue disorders	
Stevens-Johnson syndrome[3]	Rare
Blood and lymphatic system disorders	
Hypofibrinogenemia	Common
Hepatobiliary disorders[4]	

Adverse reaction (MedDRA)	Frequency Category
Drug-induced liver injury	Rare
Hepatitis	Rare
Hepatic failure	Rare
Jaundice	Rare

[1] See section *4.3 Contraindications*
[2] See section *4.4 Special warnings and precautions for use*
[3] This adverse reaction was identified through post marketing surveillance but not observed in controlled clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to Actemra in clinical trials.
[4] Frequency categories calculated based on all-exposure data obtained from relevant completed clinical trials for all indications.

Respiratory, thoracic and mediastinal disorders: There have been reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Blood and lymphatic system disorders: very rare reports of pancytopenia have occurred.

Gastrointestinal disorder: pancreatitis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE
There are limited data available on overdose with Actemra. 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.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors, ATC code: L04AC07

Mechanism of Action
Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. IL-6 is a multi-functional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including rheumatoid arthritis (RA).

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.

Pharmacodynamic effect

In clinical studies with Actemra in RA, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A and fibrinogen were observed. Rapid increases in haemoglobin levels (within the first 2 weeks) were also observed, through Actemra decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In patients with giant cell arteritis (GCA), similar rapid decreases in CRP and ESR were observed along with slight increases in mean corpuscular haemoglobin concentration.

In healthy subjects administered Actemra in doses from 2 to 28 mg/kg, absolute neutrophil counts (ANC) decreased to their lowest levels 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Patients with RA and GCA demonstrated a similar pattern of absolute neutrophil counts following Actemra administration (see section 4.4 Special warnings and precautions for use - Haematological Abnormalities).

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

The PK/PD relationship between Actemra and the sIL-6R was characterized by a popPK-sIL-6R analysis describing the duration of 90% saturation of sIL-6R in patients with COVID-19.

In addition to the body weight effect on the linear clearance of intravenous Actemra, population PK analysis identified disease severity as a significant covariate impacting both the pharmacokinetics of intravenous Actemra and the elimination rate of the TCZ-sIL-6R complex.

A sIL-6R occupancy of at least 90 % was maintained over approximately 3 weeks in patients requiring supplemental oxygen ((i.e., patients in Category 3 of the 7-category ordinal scale), and at least 2 weeks in patients presenting with the most severe COVID-19 pneumonia (i.e., patients in Category 6 of the 7-category ordinal scale) following one dose of TCZ IV 8 mg/kg. The duration of 90% sIL-6R saturation increased up to approximately 4 weeks following the administration of a second dose of TCZ IV 8 mg/kg 24 hours apart for patients in Category 3, and up to approximately 3 weeks for patients in Category 6.

For patients with BW $\geq$ 100 kg administered with one dose of 800 mg Actemra IV, the duration of 90% sIL-6R occupancy was maintained for at least 2 weeks for patients with a BW up to 180 kg. Following the administration of a second dose of 800 mg 24 hours apart, the duration of 90 % sIL-6R occupancy increased up to approximately 4 weeks and 3 weeks for patients with a BW of 100 kg and 180 kg, respectively.

Clinical trials

Rheumatoid Arthritis

The efficacy of intravenous Actemra in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multi-centre studies (Studies I – V). The efficacy of subcutaneous Actemra was assessed in two randomised, double-blind studies (Studies VI and VII). In addition, the efficacy of intravenous Actemra has been evaluated in patients with

MTX-naïve, early RA (Study VIII) and as a monotherapy versus adalimumab monotherapy (Study IX).

Studies I-V required patients ≥ age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria who had at least 8 tender and 6 swollen joints at baseline.

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

Study I (AMBITION) 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 Actemra were given every 4 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 (LITHE), a 2 year study, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of Actemra or placebo were given every 4 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 (OPTION) evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of Actemra or placebo were given every 4 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study IV (TOWARD) evaluated 1220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg Actemra or placebo were given every 4 weeks, in combination with the stable DMARD. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study V (RADIATE) evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more anti-tumour necrosis factor (TNF) therapies. The anti-TNF agent was discontinued prior to randomisation. Doses of 4 or 8 mg/kg of Actemra or placebo were given every 4 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

The efficacy and safety of subcutaneously administered Actemra was assessed in two double-blind, controlled, multi-centre studies in patients with active RA.

Study VI (SUMMACTA) was a non-inferiority study that compared the efficacy and safety of subcutaneous Actemra 162 mg administered every week to intravenous Actemra 8 mg/kg every 4 weeks. In SUMMACTA, 1262 patients were randomised 1:1 to receive subcutaneous Actemra 162 mg every week or intravenous Actemra 8 mg/kg every 4 weeks in combination with DMARD(s).

Study VII (BREVACTA) was a placebo-controlled superiority study that evaluated the safety and efficacy of subcutaneous Actemra 162 mg administered every other week to placebo. In BREVACTA, 656 patients were randomised 2:1 to subcutaneous Actemra 162 mg every other week or placebo, in combination with DMARD(s).

The primary endpoint in both studies was the proportion of patients who achieved an ACR20 response at Week 24. Both SUMMACTA and BREVACTA required patients to be ≥ 18 years of age with moderate to severe active RA diagnosed according to ACR criteria. Patients had at least 4 tender and 4 swollen joints at baseline (SUMMACTA) or at least 8 tender and 6 swollen joints at baseline (BREVACTA), and an inadequate response to their existing DMARD therapy. Approximately 20% also had a history of inadequate response to at least one TNF inhibitor. All patients in both SC studies received background non-biological DMARD(s).

The percent of patients achieving ACR 20, 50 and 70 responses in Studies I to V are shown in Table 4.

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

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

ACT = Actemra
* p < 0.05, Actemra vs. placebo + MTX/DMARD
** p < 0.01, Actemra vs. placebo + MTX/DMARD
*** p < 0.0001, Actemra vs. placebo + MTX/DMARD
† MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more. Note: the comparison for MCR occurred after the break in the hierarchical ordered testing sequence, so no

significance claims can be made. Secondary efficacy endpoints were tested in a fixed sequence approach in order to control for the rate of false positive conclusions.
^ - based on a protocol-specified interim analysis

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

In the 8 mg/kg Actemra-treated patients significant improvements were noted on all individual components of the ACR response: tender and swollen joint counts; pain assessment and CRP normalisation; disability index scores; patients and physician global assessment, compared to patients receiving placebo + MTX/DMARDS in all studies. Actemra 8 mg/kg treated patients had a statistically significant greater reduction in disease activity score (DAS28) than patients treated with placebo + DMARD. The rate of remission (defined as DAS < 2.6) for patients treated with Actemra ranged from 27.5% to 33.6%. Actemra treated patients had a statistically significant greater rate of remission than patients treated with placebo + DMARD. A good to moderate EULAR response was achieved by significantly more Actemra treated patients compared to patients treated with placebo + DMARD (Table 5).

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

ACT = Actemra
†The p value compares across all the EULAR categories
* p < 0.05, Actemra vs. placebo + MTX/DMARD
** p < 0.01, Actemra vs. placebo + MTX/DMARD
*** p < 0.0001, Actemra vs. placebo + MTX/DMARD
≠ In study II, 47% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 33% of patients at week 24.
^ In study II, 8% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 4% of patients at week 24.

The clinical response to 24 weeks of subcutaneous Actemra therapy is shown in Table 6. In SUMMACTA, the primary outcome measure was ACR20 at Week 24. The pre-specified non-

inferiority margin was a treatment difference of 12%. The study demonstrated non-inferiority of Actemra with respect to ACR20 at Week 24; ACR50, ACR70 and DAS28 responses are also shown in Table 6. The efficacy and safety of subcutaneous Actemra used as a monotherapy is supported by SUMMACTA which demonstrates, in combination with DMARD(s), the non-inferiority of Actemra 162 mg SC every week to 8 mg/kg IV every 4 weeks. However, the efficacy of subcutaneous Actemra administered every week as a monotherapy was not directly established in this study.

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

	Study VI (SUMMACTA)[a]		**Study VII (BREVACTA)[b]**	
	ACT SC 162 mg every week + DMARD(s)	**ACT IV 8 mg/kg every 4 weeks + DMARD(s)**	**ACT SC 162 mg every other week + DMARD(s)**	**Placebo + DMARD(s)**
	n=558	**n=537**	**n=437**	**n=219**
ACR20				
Week 24	69.4%	73.4%	60.9%	31.5%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)		30 (22.0, 37.0)	
ACR50				
Week 24	47.0%	48.6%	39.8%	12.3%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)		28 (21.5, 34.4)	
ACR70				
Week 24	24.0%	27.9%	19.7%	5.0%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)		15 (9.8, 19.9)	
Change in DAS28 [adjusted mean]				
Week 24	-3.5	-3.5	-3.1	-1.7
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)		-1.4 (-1.7, -1.1)	
DAS28 < 2.6 response (%)				
Week 24	38.4%	36.9%	32.0%	4.0%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)		28.6 (22.0, 35.2)	

ACT = Actemra
[a] = per protocol population
[b] = intent to treat population

In SUMMACTA, ACR 20, 50 and 70 response rates were comparable between the subcutaneous and intravenous Actemra study arms across the three body weight categories (< 60 kg, 60 – 100 kg, ≥ 100 kg). ACR 20, 50 and 70 response rates in the heaviest weight category (≥ 100 kg) were lower compared to the other weight categories in the subcutaneous and intravenous Actemra study arms. The same phenomenon of lower response rates in heavier patients (≥ 100 kg) compared to other weight categories was seen in patients receiving the subcutaneous Actemra every other week regimen in BREVACTA.

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

Radiographic response

In study II (LITHE), 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 (JSN) score. Missing week 52 radiographic data was imputed using linear extrapolation. This was performed for any patient who had a baseline assessment and at least one post-baseline radiographic assessment. The change from baseline was then calculated using the extrapolated score. Inhibition of structural joint damage was shown with significantly less radiographic progression in patients receiving Actemra compared to control (Table 7).

In the open-label extension of study II further improvement in the inhibition of progression of structural damage in Actemra + MTX-treated patients were observed in the second year of treatment. Study II did not investigate the effect of Actemra monotherapy on radiographic endpoints.

Table 7 Radiographic mean changes at 52 and 104 weeks in study II (LITHE)

	ACT 8 mg/kg + MTX **n=398**	**Placebo + MTX (+ option of ACT from week 16)** **n=393**
Changes from baseline to week 52		
n	353	294
Total Sharp-Genant score	0.25	1.17
Erosion score	0.15	0.76
JSN score	0.10	0.41
Change from week 52 to week 104		
n	353	294
Total Sharp-Genant score	0.12	0.79
Erosion score	0.07	0.48
JSN score	0.05	0.31

ACT = Actemra
JSN = joint space narrowing
The data presented 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 the week 104 visit.

Following 1 year of treatment with Actemra + MTX, 83% of patients had no progression of structural damage, as defined by a change in the Total Sharp 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.

In Study VII (BREVACTA), 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 subcutaneous Actemra compared with placebo; mean change from baseline in mTSS of 0.62 vs. 1.23 (p = 0.0149; van Elteren) with an adjusted mean difference of -0.60 (-1.1, -0.1). These results are consistent with those observed in patients treated with intravenous Actemra.

Quality of Life Outcomes
Clinically significant improvements in disability index (HAQ-DI, Health Assessment Questionnaire Disability Index), fatigue (FACIT-F, Functional Assessment of Chronic Illness

Therapy Fatigue) and improvement in both the physical (PCS, Physical Component Summary) and mental health (MCS, Mental Component Summary) domains of the SF-36 (Short Form 36) were observed in patients treated with 8 mg/kg Actemra (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs.

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

At week 52, the mean change in HAQ-DI was -0.58 in the Actemra 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 Actemra 8 mg/kg + MTX group (-0.61). The percentage of Actemra-treated patients showing a clinically relevant improvement in HAQ-DI (≥ 0.3 units) at weeks 52 & 104 were 63% and 62%, respectively.

In Study VI (SUMMACTA), the mean decrease in HAQ-DI from baseline to week 24 was 0.6 for both subcutaneous Actemra 162 mg weekly and intravenous Actemra 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 subcutaneous Actemra every week group (65.2%) versus the intravenous Actemra 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. In Study VII (BREVACTA), the mean decrease in HAQ-DI from baseline to week 24 was 0.4 and 0.3, and the proportion of patients who achieved a clinically relevant improvement in HAQ-DI was 58% and 47%, for the subcutaneous Actemra 162 mg every other week, and placebo treatment groups, respectively.

Laboratory Evaluations

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

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

MTX naive, Early RA

Study VIII (FUNCTION), 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) and one or more indicators of poor prognosis, such as elevated inflammatory markers (e.g. ESR and/or CRP), the presence of RF and/or anti-CCP, and/or the presence of bony erosions attributable to RA. This study evaluated the efficacy of intravenous Actemra 4 or 8 mg/kg every 4 weeks in combination with MTX, Actemra 8 mg/kg

monotherapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage for 104 weeks. The primary endpoint was the proportion of patients achieving DAS28 remission (DAS28 < 2.6) at week 24. A significantly higher proportion of patients in the Actemra 8 mg/kg + MTX and Actemra monotherapy groups met the primary endpoint compared with MTX alone. The Actemra 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the Actemra 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints (although the differences between Actemra 8 mg/kg monotherapy and MTX were not statistically significant). The results from study VIII are shown in Table 8.

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

			ACT 8 mg/kg + MTX n=290	**ACT 8 mg/kg + placebo n=292**	**Placebo + MTX n=287**
Primary Endpoint					
DAS < 2.6 response (%)					
Week 24			44.8***	38.7***	15.0
Key Secondary Endpoints					
DAS < 2.6 response (%)					
Week 52			49.0***	39.4	19.5
ACR (%)					
Week 24	ACR20		74.5*	70.2	65.2
		ACR50	56.9**	47.6	43.2
		ACR70	38.6**	30.1	25.4
Week 52	ACR20		67.2*	63.0	57.1
		ACR50	55.9**	49.3	40.8
		ACR70	43.1**	36.0	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 (%) (change from baseline in mTSS[#] of ≤ 0)		83[‡]	82[‡]	73

All efficacy comparisons vs Placebo + MTX. ***p ≤ 0.0001; **p < 0.001; *p < 0.05;
[#] mTSS = modified Total Sharp score

Actemra versus adalimumab in monotherapy

Study IX (ADACTA) evaluated 326 patients with RA who were intolerant of MTX or in whom continued treatment with MTX was considered inappropriate, which included patients considered to be MTX inadequate responders. Patients in the Actemra arm received an intravenous (IV) infusion of Actemra (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w.

A statistically significant superior treatment effect was seen in favour of Actemra over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 9).

Table 9 Efficacy Results for Study IX (ADACTA)

	ADA + Placebo (IV) n=162	ACT + Placebo (SC) n=163	p-value[a]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	-1.8	-3.3	
Difference in adjusted mean (95% CI)	-1.5 (-1.8, -1.1)		<0.0001
Secondary Endpoints - Percentage of Responders at Week 24 [(b)]			
DAS28 < 2.6, n (%)	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 randomised, open-label (sponsor-blinded), 2-arm parallel-group, multi-centre, 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 Actemra compared with a TNF inhibitor standard of care (etanercept).

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 randomised 1:1 to IV Actemra 8 mg/kg every four weeks (q4w) or SC etanercept 50 mg every week (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 Actemra to etanercept for cardiovascular risk was determined by excluding a > 80% relative increase in the risk of MACE. The primary endpoint was met with a hazard ratio [HR] comparing Actemra to etanercept = 1.05; 95% CI = 0.77, 1.43.

Giant Cell Arteritis (GCA)

Study X (GiACTA) was a randomised, multi-centre, double-blind, placebo-controlled Phase III superiority study conducted to assess the efficacy and safety of Actemra in patients with GCA.

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

Two subcutaneous (SC) doses of Actemra (162 mg every week and 162 mg every other week) were compared to two different placebo control groups randomised 2:1:1:1. All patients received background glucocorticoid (prednisone) therapy. Each of the Actemra-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.

The study included adult patients with new-onset or relapsing active GCA, where active GCA was defined as the presence of clinical signs and symptoms of GCA (cranial or polymyalgia rheumatica) and ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL within 6 weeks prior to the baseline visit. New-onset disease was defined as GCA diagnosed within 6 weeks of baseline, and relapsing disease was defined as GCA diagnosed > 6 weeks before baseline and previous treatment with ≥ 40 mg/day prednisone for ≥ 2 consecutive weeks. The majority of the enrolled population were Caucasian (96.8%) and a majority were female (74.9%). The mean age of patients was 69 years. Relapsing disease patients comprised 53% of the study population with 47% of patients presenting with new-onset disease. The most common clinical manifestations of GCA at diagnosis were headache and polymyalgia rheumatica (in 67% and 62% patients, respectively). Jaw claudication and scalp tenderness were reported in approximately one third of patients. Temporal artery tenderness was observed in 29%, decreased temporal artery pulsation in 12%, and ischemia-related vision loss in 10% of patients.

The primary efficacy endpoint, assessed by the proportion of patients achieving steroid-free sustained remission at Week 52 on Actemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 10).

Secondary Endpoints
The key secondary efficacy endpoint, also based on the proportion of patients achieving sustained remission at Week 52, comparing Actemra plus 26 weeks prednisone taper with the longer placebo plus 52 weeks prednisone taper, was also met (Table 10). A statistically significant superior treatment effect was seen in favour of Actemra over placebo in achieving steroid-free sustained remission at Week 52 on Actemra 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 10.

The assessment of the time to first GCA flare showed a significantly lower risk of flare for the Actemra weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the Actemra every other week group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). Actemra 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 10).

The median cumulative prednisone dose at Week 52 was significantly lower in the two Actemra dose groups compared to the two placebo groups (Table 10). 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 Actemra weekly and every other week 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. A lower proportion of patients stopped the protocol defined prednisone taper and moved onto treatment with escape

prednisone in the Actemra weekly (23.0%) and Actemra every-other-week (32.7%) groups compared with patients in the placebo plus 52 weeks prednisone taper (54.9%) and placebo plus 26 weeks prednisone taper (74.0%) groups. Median prednisone starting dose for the escape patient population was 30.0 mg in each of the Actemra weekly, Actemra every-other-week and placebo plus 26 weeks prednisone taper groups and 37.5 mg in the placebo plus 52 weeks prednisone taper group. There was no consistent pattern to the time of initiation of escape therapy.

Table 10 Efficacy Results from Study X (GiACTA)

			PBO + 26 weeks prednisone taper n=50	**PBO + 52 weeks prednisone taper n=51**	**ACT 162mg SC QW + 26 weeks prednisone taper n=100**	**ACT 162 mg SC Q2W + 26 weeks prednisone taper n=49**
Primary Endpoint *Sustained remission (ACT groups vs PBO+26)* Responders at Week 52, n (%)			7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions			N/A	N/A	42%*	39.06%*
(99.5% CI)					(18.00, 66.00)	(12.46, 65.66)
Key Secondary Endpoint *Sustained remission (ACT 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]*						
All patients	ACT vs. PBO+26	HR	N/A	N/A	0.23*	0.28**
		(99% CI)			(0.11, 0.46)	(0.12, 0.66)
	ACT vs. PBO+52	HR	N/A	N/A	0.39**	0.48
		(99% CI)			(0.18, 0.82)	(0.20, 1.16)
Relapsing patients	ACT vs. PBO+26	HR	N/A	N/A	0.23***	0.42
		(99% CI)			(0.09,0.61)	(0.14, 1.28)
	ACT vs. PBO+52	HR	N/A	N/A	0.36	0.67
		(99% CI)			(0.13, 1.00)	(0.21,2.10)
New-onset patients	ACT vs. PBO+26	HR	N/A	N/A	0.25***	0.20***
		(99% CI)			(0.09, 0.70)	(0.05, 0.76)
	ACT vs. PBO+52	HR	N/A	N/A	0.44	0.35

	PBO + 26 weeks prednisone taper n=50	PBO + 52 weeks prednisone taper n=51	ACT 162mg SC QW + 26 weeks prednisone taper n=100	ACT 162 mg SC Q2W + 26 weeks prednisone taper n=49
(99% CI)			(0.14, 1.32)	(0.09, 1.42)
Cumulative glucocorticoid dose (mg)				
Median at Week 52 (ACT groups vs PBO+26[2])	3296	N/A	1862.00*	1862.00**
Median at Week 52 (ACT groups vs PBO+52[2])	N/A	3817.5	1862.00*	1862.00*
Exploratory Endpoints				
Annualized relapse rate, Week 52§				
Mean (SD)	1.74 (2.18)	1.3 (1.84)	0.41 (0.78)	0.67 (1.1)

* 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, ACT = Actemra, PBO = placebo, QW = every week dose, Q2W = every other week dose

Quality of Life Outcomes

In Study X, 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 Actemra weekly and every other week dose groups [4.10, 2.76, respectively] than in the two placebo groups [placebo plus 26 weeks; -0.28, placebo plus 52 weeks; -1.49], although only the comparison between Actemra 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 Actemra weekly and every other week 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 week]) 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 Actemra weekly and every other week dose groups [-19.0, -25.3, respectively] than in both placebo groups [placebo plus 26 weeks; -3.4, placebo plus 52 weeks; -7.2], although only the Actemra every other week plus 26 weeks prednisone taper group showed a statistically significance difference compared to placebo [placebo plus 26 weeks taper p = 0.0059, and placebo 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: Actemra weekly 5.61 [10.115], Actemra every other week 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 Actemra weekly 0.10 [0.198], Actemra every other week 0.05 [0.215], placebo 0.07 [0.293], and placebo plus 52 weeks -0.02 [0.159].

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

COVID-19

RECOVERY
RECOVERY is a randomised evaluation of COVID-19 therapy. This study is a collaborative group study in hospitalised adults diagnosed with COVID-19.

RECOVERY was a large, randomised, controlled, open-label, multi-centre platform study conducted in the United Kingdom to evaluate the efficacy and safety of potential treatments in hospitalised adult patients with severe COVID-19. All eligible patients received usual care and underwent an initial (main) randomisation. 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 randomisation to receive either intravenous Actemra or usual care alone.

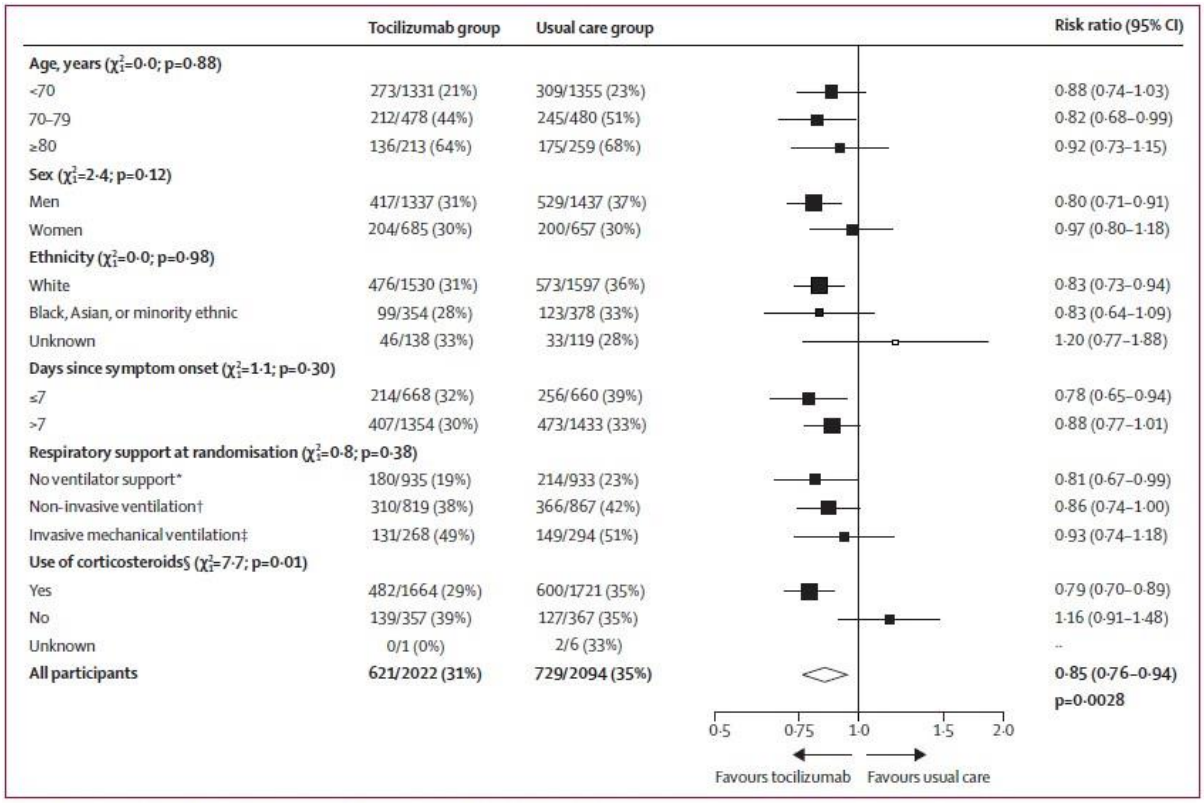
Efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 patients who were randomised with 2022 patients in the Actemra + usual care arm and 2094 patients in the usual care alone arm. The baseline demographic and disease characteristics of the ITT population were well 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 Actemra + 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 Actemra 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. Based on this mortality reduction, 25 treated patients are needed to save one life. 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). Within the subgroup of patients receiving systemic corticosteroids, 17 treated patients are needed to save one life.

The median time to hospital discharge was 19 days in the Actemra + 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 Actemra + 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).

Figure 2 RECOVERY trial – Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics



Study ML42528 (EMPACTA)

Study ML42528 was a global Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy and safety of intravenous Actemra in combination with standard of care (SoC), in hospitalised, 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 randomised at a 2:1 ratio to receive one infusion of either 8 mg/kg Actemra 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 Actemra or placebo could be given, 8–24 hours after the initial infusion.

Of the 389 patients who were randomised, 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 Actemra 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 randomisation, 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 Actemra, 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 Actemra 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 Actemra 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 Actemra arm versus 8.6% in the placebo arm (weighted difference (Actemra arm - placebo arm): 2.0% [95% CI, -5.2% to 7.8%]). Mortality at Day 60 (post-hoc analysis) was 11.2% in the Actemra arm versus 10.9% in the placebo arm (weighted difference (Actemra arm - placebo arm): 0.5% [95% CI, -6.9% to 6.8%]).

Study WA42380 (COVACTA)
Study WA42380 was a global Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy and safety of intravenous Actemra, in combination with standard of care (SoC), in adult patients hospitalised 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 randomised at a 2:1 ratio to receive one infusion of either 8 mg/kg Actemra, 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 Actemra or placebo could be given, 8–24 hours after the initial infusion.

Of the 452 patients who were randomised, 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 Actemra 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 randomisation, 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

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 Actemra arm to the placebo arm. The median clinical status category at Day 28 was 1.0 in the Actemra 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 Actemra 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 Actemra arm versus 19.4% in the placebo arm (weighted difference (Actemra arm - placebo arm) Day 28: 0.3% [95% CI, -7.6 to 8.2]. Mortality at Day 60 was 24.5% in the Actemra arm versus 25.0% in the placebo arm (weighted difference (Actemra arm - placebo arm): -0.5% [95% CI, -9.1 to 8.0]).

Study WA42511 (REMDACTA)
Study WA42511 was a global, Phase III, randomised, double-blind, placebo-controlled, multi-centre study conducted to assess the efficacy and safety of intravenous Actemra in combination with remdesivir (RDV) compared with matching placebo in combination with RDV in hospitalised 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 randomised at a 2:1 ratio to receive blinded treatment of either Actemra + 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 Actemra + RDV arm received one infusion of Actemra 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 Actemra or placebo could be given, 8–24 hours after the initial infusion.

Of the 649 patients who were randomised, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of all patients who received any amount of Actemra / placebo (430 in the Actemra + 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 randomisation, 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

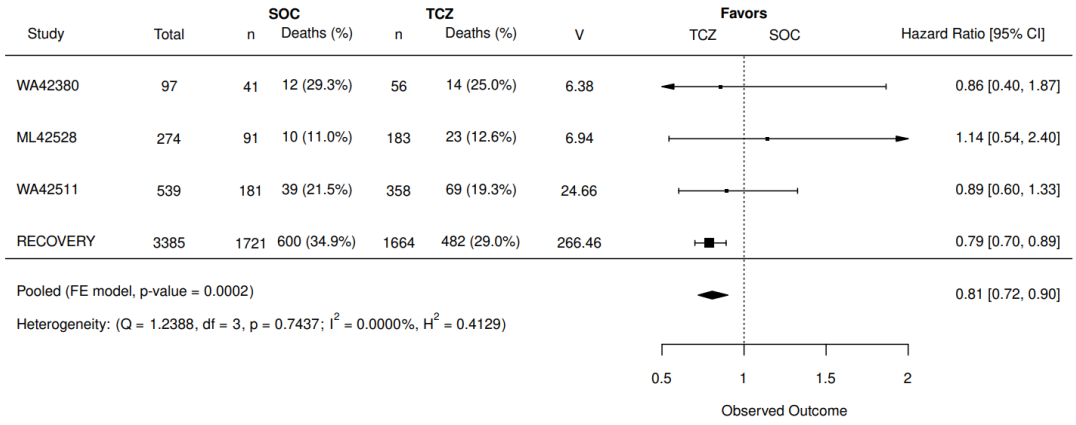
symptom onset was 8 days. At baseline, the majority of patients received corticosteroids (84.2% across treatment arms). The median (range) levels of CRP and ferritin were 98.20 mg/L (1.3 - 418.3) and 2.13 pmol/mL (0.1-30.8), respectively. The most common comorbidities were hypertension (61.7%), diabetes (39.5%) and obesity (27%).

The primary efficacy endpoint was time from randomisation 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 Actemra arm versus 19.5% in the placebo arm (weighted difference (Actemra arm - placebo arm): -1.3% [95% CI, -7.8% to 5.2%]). Mortality at Day 60 was 22.6% in the Actemra arm versus 25.7% in the placebo arm (weighted difference (Actemra 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 (Actemra: 597 and placebo: 313 from Roche trials, Actemra: 1664 and standard of care 1721 from RECOVERY). The combined HR showed that Actemra 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 3 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

Intravenous administration
The efficacy of intravenous Actemra was assessed in a three-part study including an open-label extension in children with moderately to severely active pJIA, who had an inadequate response

to methotrexate (MTX) or inability to tolerate MTX (Study XI, CHERISH). Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least 5 joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints). The patients treated had subtypes of JIA that at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of MTX was permitted but was not required during the study. Concurrent use of DMARDs other than MTX, or other biologics (e.g. TNF antagonists or T cell costimulation modulator) were not permitted in the study. Ten patients who participated in the study were less than 4 years of age.

Part I consisted of a 16 week active Actemra 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 Actemra at 8 mg/kg for 4 doses. Patients < 30 kg were randomised 1:1 to receive either Actemra 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline entered the blinded withdrawal period (Part II) of the study. In Part II, patients were randomised to Actemra (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX 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. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% 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 Actemra-treated patients. These proportions were statistically significantly different (p=0.0024).

At the conclusion of Part I, JIA ACR 30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.

During the withdrawal phase (Part II), the percentages of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in the table below.

Table 11 JIA ACR response rates at week 40 relative to baseline (percentages of patients)

Response Rate	**Actemra n=82**	**Placebo n=81**
JIA ACR 30	74.4%†	54.3%†
JIA ACR 50	73.2%†	51.9%†
JIA ACR 70	64.6%†	42.0%†

† p<0.001, Actemra vs. placebo

A difference in the incidence of JIA ACR30 flare during Week 16 to 40 was observed between those patients who were and were not taking concurrent MTX, and those patients who had previously been exposed to a biologic DMARD or not. Irrespective of concurrent MTX or previous biologic DMARD use JIA ACR30 flare was lower for patients receiving Actemra compared to placebo (Table 12).

Table 12 Proportion of patients with a JIA ACR30 Flare at Week 40 by background MTX use at baseline or prior biologic DMARD use

	Placebo		Actemra	
MTX Use	**Yes (n=64)**	**No (n=17)**	**Yes (n=67)**	**No (n=15)**
JIA ACR30 Flare	25 (39.1%)	14 (82.4%)	13 (19.4%)	8 (53.3%)
Prior Biologic Use	**Yes (n=23)**	**No (n=58)**	**Yes (n=27)**	**No (n=55)**
JIA ACR30 Flare	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)

In Part III maintenance of efficacy through Week 104 was demonstrated for each of the JIA responses rates and were similar between the continuous Actemra-treated subgroup and the placebo-treated patients in Part II who re-commenced Actemra. For the continuous Actemra group the JIA ACR 30/50/70/90 response rates at Week 104 were 95.1%, 90.2%, 86.6% and 70.7%, respectively. For placebo-treated patients in Part II who re-commenced Actemra JIA ACR 30/50/70/90 response rates at Week 104 were 95.1%, 95.1%, 91.4%, and 66.7%, respectively. Improvement in JIA ACR core components observed at Week 40 was maintained.

Subcutaneous Administration
A 52-week, open-label, multi-centre, PK-PD and safety study (Study XI, JIGSAW) was conducted in paediatric patients with pJIA, aged 1 to 17 years old.

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

The SC Actemra 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 Actemra regimens for pJIA.

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

<u>Systemic Juvenile Idiopathic Arthritis</u>

Intravenous administration
The efficacy of intravenous Actemra for the treatment of active sJIA was assessed in a 12-week randomised, double blind, placebo-controlled, parallel group, 2-arm study (Study XII, TENDER). Patients (treated with or without MTX) were randomised (Actemra: placebo = 2:1) to one of two treatment groups. 75 patients received Actemra infusions every two weeks either 8 mg/kg for patients ≥ 30kg or 12 mg/kg for patients < 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering could occur from week 6 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 demographic characteristics at baseline were similar between the placebo and Actemra groups. Patients were evenly split between male and female, with a median age of 9 and 10 for the placebo and Actemra groups, respectively. 27 patients in the study were aged between 2-5 years, 48 patients between 6-12 years and 37 patients between 13-18 years. Baseline disease characteristics studied included fever and rash status, previous use of DMARDs, previous use

of biologics, CRP, and articular and extra-articular damage. All were similar between the placebo and Actemra groups except for a higher proportion of patients with rash in the placebo group (48.6%) compared with the Actemra group (29.3%). In addition, baseline CRP was lower in the placebo group in comparison with the Actemra group.

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 Actemra and 24.3% (9/37) of placebo patients achieved this endpoint. These proportions were highly significantly different (p<0.0001).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in the table below.

Table 13 JIA ACR response rates at week 12 (percent of patients)

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

* p<0.0001, Actemra vs. placebo

Secondary endpoints of the study included the proportion of patients with fever due to sJIA at baseline who were free of fever at week 12, corticosteroid tapering, quality of life improvements as measured by CHAQ-DI and changes in laboratory parameters.

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

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

Corticosteroid Tapering
Of the 31 placebo and 70 Actemra patients receiving oral corticosteroids at baseline, 8 placebo and 48 Actemra patients achieved a JIA ACR70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) Actemra patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12 (p=0.028).

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

Laboratory Parameters

Fifty out of 75 (67%) patients treated with Actemra had a haemoglobin < LLN at baseline. Forty (80%) of these patients with decreased haemoglobin had an increase in their haemoglobin to within the normal range at week 12, in comparison to only 2 out of 29 (7%) of placebo patients with haemoglobin < LLN at baseline ($p < 0.0001$). Forty-four (88%) Actemra patients with decreased haemoglobin at baseline had an increase in their haemoglobin by ≥ 10 g/L at week 6 versus 1 (3%) placebo patient ($p < 0.0001$).

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

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

Subcutaneous administration
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 Actemra that achieved comparable PK/PD and safety profiles to the IV regimen.

Eligible patients received Actemra dosed according to body weight (BW), with patients weighing ≥ 30 kg (n=26) dosed with 162 mg of Actemra every week (QW) and patients weighing below 30 kg (n = 25) dosed with 162 mg of Actemra 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 Actemra and 25 (49%) had been receiving IV Actemra and switched to SC Actemra at baseline.

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

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

The efficacy population for the tisagenlecleucel cohort included 28 males and 23 females (total 51 patients) of median age 17 years (range, 3–68 years). The median time from start of CRS to first dose of Actemra was 3 days (range, 0–18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Patients were considered responders if CRS resolved within 14 days of the first dose of Actemra, if no more than 2 doses of Actemra were needed, and no drugs other than Actemra and corticosteroids were used for treatment. Thirty-nine patients (76.5%; 95% CI: 62.5%–87.2%) achieved a response. In an independent cohort of 15 patients (range: 9–75 years old) with axicabtagene ciloleucel-induced CRS, 53% responded.

5.2 PHARMACOKINETIC PROPERTIES

Rheumatoid Arthritis
Intravenous Administration

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

The pharmacokinetic parameters of Actemra did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{min}) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration (C_{max}) increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 2.7 and 6.5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The following parameters are valid for a dose of 8 mg/kg Actemra given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of Actemra were 35000 ± 15500 h·µg/mL, 9.74 ± 10.5 µg/mL, and 183 ± 85.6 µg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Actemra AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of Actemra were 55500 ± 14100 h·µg/mL, 19.0 ± 12.0 µg/mL, and 269 ± 57 µg/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, Actemra doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see section 4.2 Dose and Method of Administration).

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

Subcutaneous Administration

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

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

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

Giant Cell Arteritis (GCA)

The pharmacokinetics of Actemra in GCA patients were determined using a population pharmacokinetic 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 14 Predicted mean ± SD PK parameters at steady-state after SC dosing in GCA

	SC	
Actemra 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

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

COVID-19

The pharmacokinetics of Actemra in COVID-19 adult patients was characterised 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 15. 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 Actemra. With a dosing regimen of 8 mg/kg Actemra with a maximum dose of 800 mg Actemra, 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 Actemra in polyarticular juvenile idiopathic arthritis (pJIA) patients were characterised using 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 16 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 (body weight < 30 kg), and by Week 16 for the 8 mg/kg (body weight ≥ 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.

Caution is advised with interpretation of the model-derived PK results as the model under predicted $C_{trough.ss}$ after SC dosing in the body weight <30 kg group by greater than 30%.

Systemic Juvenile Idiopathic Arthritis

The pharmacokinetics of Actemra in sJIA patients was characterised by a population pharmacokinetic analysis which included 140 patients who were treated with 8 mg/kg IV every 2 weeks (patients weighing ≥ 30 kg), 12 mg/kg IV every 2 weeks (patients weighing below 30 kg), 162 mg SC every week (patients weighing ≥ 30 kg), 162 mg SC every 10 days or every 2 weeks (patients weighing below 30 kg). Limited data are available regarding exposures following subcutaneous administration of Actemra in sJIA patients below 2 years of age and in sJIA patients who weigh less than 10 kg. Three patients aged 1-2 were included in Study WA28118.

Patients with sJIA must have a minimum body weight of 10 kg when receiving Actemra subcutaneously (see section 4.2 Dose and Method of Administration).

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

	IV		SC	
Actemra 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.

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 Actemra weekly dose and 4.5 days after the Actemra every other week dose.

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

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

Distribution

Following IV dosing, Actemra undergoes biphasic elimination from the circulation. In RA patients the central volume of distribution was 3.5 L and 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 paediatric patients with pJIA, the central volume of distribution was 1.98 L, the peripheral volume of distribution was 2.1 L, resulting in a volume of distribution at steady state of 4.08 L.

In paediatric patients with sJIA, the central volume of distribution was 1.87 L and 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.

Metabolism

Not applicable.

Excretion

The total clearance of Actemra was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in RA patients, 6.7 mL/h in GCA

patients, 5.8 mL/h in paediatric patients with pJIA and 5.7 mL/h in paediatric patients with sJIA. The concentration-dependent nonlinear clearance plays a major role at low Actemra concentrations. Once the nonlinear clearance pathway is saturated, at higher Actemra concentrations, clearance is mainly determined by the linear clearance. Due to dependence of total clearance on Actemra serum concentrations, $t_{1/2}$ of Actemra is also concentration-dependent and can only be calculated at a given serum concentration level.

In RA patients, for intravenous administration, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration, the concentration-dependent apparent t1/2 is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state. At high serum concentrations, when total clearance of Actemra is dominated by linear clearance, a terminal t1/2 of approximately 21.5 days was derived from the population parameter estimates.

In GCA patients, at steady state, the effective $t_{1/2}$ of Actemra 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 week regimen. At high serum concentrations, when total clearance of Actemra 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 Actemra 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 Actemra in children with pJIA 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 estimated effective $t_{1/2}$ of Actemra 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 $t_{1/2}$ of IV Actemra 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 $t_{1/2}$ of Actemra in sJIA patients is up to 14 days for both the 162 mg QW and Q2W regimens during a dosing interval at steady state.

Pharmacokinetics in Special Populations

Hepatic Impairment

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

Renal Impairment

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

Most of the patients in the RA and GCA studies in the 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 Actemra. Actemra has not been studied in patients with moderate to severe renal impairment. (see section 5.1 Pharmacodynamic Properties, Clinical Trials and section 4.2 Dose and Method of Administration).

Approximately one-third of the patients in the Study X (GiACTA) had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on Actemra exposure was noted in these patients.

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

Other special populations
Population pharmacokinetics in adult RA, GCA and COVID-19 patients showed that age, sex and race did not affect the pharmacokinetics of Actemra. No dose adjustment is necessary for these demographic factors.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

A carcinogenicity study of Actemra has not been conducted. Proliferating lesions were not observed in a chronic cynomolgus monkey 6-month toxicity study.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Concentrated solution for intravenous infusion

Actemra® - AUST R 149402, AUST R 149403, AUST R 149404

Polysorbate 80
Sucrose
Dibasic sodium phosphate dodecahydrate
Monobasic sodium phosphate dihydrate
Water for injections

Solution for subcutaneous injection

Actemra® - AUST R 234034, AUST R 296808:

Histidine
Histidine hydrochloride monohydrate
Polysorbate 80
Arginine
Arginine hydrochloride
Methionine
Water for injections

Actemra® SC – AUST R 370314, AUST R 370315:

Histidine
Histidine hydrochloride monohydrate

Polysorbate 80
Arginine hydrochloride
Methionine
Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

The medicine should not be used after the expiry date (EXP) shown on the vial or vial carton or the pre-filled syringe or the pre-filled pen and the carton.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Concentrated solution for intravenous infusion

Store vials at 2 ºC to 8 ºC. (Refrigerate. Do not freeze.)

Keep the container in the outer carton in order to protect from light.

Actemra does not contain any antimicrobial agent; therefore, care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue.

The prepared infusion solution of Actemra is physically and chemically stable in 0.9% w/v sodium chloride solution at 30ºC for 24 hours. To reduce microbiological hazard, the prepared infusion should be used immediately. If storage is necessary, hold at 2ºC to 8ºC for not more than 24 hours.

Solution for subcutaneous injection

Store the pre-filled syringe or pen at 2 ºC to 8 ºC. (Refrigerate. Do not freeze.) Keep in carton to protect from light and keep dry.

Once removed from the refrigerator, the pre-filled syringe or pre-filled pen can be stored up to 2 weeks (14 days) at or below 30 °C. The unopened pre-filled syringe or pre-filled pen may be removed and returned to the refrigerator multiple times as long as the total cumulative storage time at or below 30°C does not exceed 14 days. The pre-filled syringe or pre-filled pen must always be kept in the carton to protect from light and keep dry.

Actemra does not contain any antimicrobial agent. Product is for single use in one patient only. Discard any residue.

6.5 NATURE AND CONTENTS OF CONTAINER

Concentrated solution for intravenous infusion

Actemra is supplied in preservative-free, non-pyrogenic single-use, clear glass vials.

Single use vial containing 80 mg of Actemra in 4 mL (20 mg/mL). Packs of 1 and 4 vials.
Single use vial containing 200 mg of Actemra in 10 mL (20 mg/mL). Packs of 1 and 4 vials.

Single use vial containing 400 mg of Actemra in 20 mL (20 mg/mL). Packs of 1 and 4 vials.

Solution for subcutaneous injection

Actemra and Actemra SC is supplied as a preservative-free, non-pyrogenic solution presented in a ready-to-use, single-use pre-filled syringe and pre-filled pen (ACTPen) with needle safety device.

Single-use pre-filled syringe with needle safety device. Each syringe contains 162 mg of Actemra in 0.9 mL. Packs of 1 and 4 syringes.

Single-use pre-filled pen (ACTPen) with needle safety device. Each pen contains 162 mg of Actemra in 0.9 mL. Available in packs of 1 and 4 pens.

Some pack sizes are not marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Disposal of syringes/pens /sharps

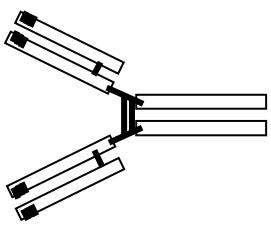
The following points should be strictly adhered to regarding the use and disposal of the pre-filled syringe and pre-filled pen:

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Actemra is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass which binds to human interleukin 6 (IL-6) receptors. It is composed of two heterodimers, each of which consists of a heavy and a light polypeptide chain. The light chain contains of 214 amino acids and the heavy chain 448 amino acids. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Actemra has a molecular weight of

approximately 148,000 Daltons. Actemra binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R).

CAS number
375823-41-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL
21 May 2009

10. DATE OF REVISION OF THE TEXT
2 September 2022

Summary table of changes

Section Changed	Summary of new information
4.8	Addition of post-marketing adverse effect pancreatitis
6.4	Update to out of fridge storage condition