Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tocilizumab

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

December 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	Extension of Indications
Decision:	Approved
Date of Decision:	31 October 2011
Active ingredient(s):	Tocilizumab
Product Name(s):	Actemra
Sponsor's Name and Address:	Roche Products Pty Ltd PO Box 255 Dee Why NSW 2099
Dose form(s):	Concentrated solution for infusion
Strength(s):	80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL
Container(s):	Single use vial
Pack size(s):	Packs of 1 and 4.
Approved Therapeutic use:	**Rheumatoid arthritis** Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients: · in combination with methotrexate (MTX) or other nonbiological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or · 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, as measured by X-ray, when given in combination with methotrexate. **Systemic Juvenile Idiopathic Arthritis** ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. ACTEMRA can be given alone or in combination with methotrexate (MTX).
Route(s) of administration:	Intravenous infusion
Dosage:	The proposed recommended dose of ACTEMRA for patients with systemic juvenile idiopathic arthritis (sJIA) is 12 mg/kg for patients < 30 kg and 8 mg/kg for patients ≥ 30 kg given once every two weeks as an IV infusion.
ARTG Number (s):	149402, 149403, 149404

Product Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive inflammatory synovitis manifested by polyarticular joint swelling. The

overproduction of pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin-1 (IL-1) and IL-6 in the joints and sera of patients with RA are important mediators in the disease pathogenesis via activation of T-lymphocytes, initiating the production of acute phase reactants, and their role in stimulation of haemopoietic cells. Tocilizumab is a recombinant humanized monoclonal antibody that binds to, and inhibits signaling mediated by soluble and membrane-bound IL-6 receptors. As such, treatment with tocilizumab inhibits the pro-inflammatory functions of IL-6.

Actemra (tocilizumab) was first considered by the Australian Drug Evaluation Committee (which preceded the Advisory Committee on Prescription Medicines, ACPM) at its 263rd meeting held on 2-3 April 2009. There was no objection to approval of the submission for the indication which is presently approved (see below). Five controlled Phase III studies were conducted to assess the efficacy and safety of tocilizumab over 24 weeks, in one study as monotherapy, combined with methotrexate (MTX) in three studies and combined with MTX and/or other disease-modifying anti-rheumatic drugs (DMARDs) in the remaining study. All five studies were multicentre, randomised, double blind, controlled studies and all had an escape arm where patients with inadequate response could, at the investigator's (blinded) request, receive adjusted therapy with tocilizumab. The primary efficacy endpoint for all of the pivotal studies was a comparison of the proportion of patients in each treatment arm with an ACR 20 response at Week 24.[1]

The current indications for Actemra are:

Actemra (tocilizumab) 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 antirheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or*
- *as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*

ACTEMRA (tocilizumab) has been shown to inhibit the progression of joint damage, as measured by X-ray, and to improve physical function.

More recently, an extension of indications was approved to add the final sentence to the approved indications.[2] This application was supported by a single pivotal study which enrolled adult patients with active RA who had an inadequate response to MTX. In particular, the trial assessed the outcomes of radiographic analyses with respect to a reduction in the progression of joint damage and data on the improvement of physical function. The application was also supported by the cumulative long term efficacy and safety data from the open label extension phase of one of the original studies as well as two ongoing open label extension studies which recruited patients from the controlled trials in the original tocilizumab registration application.

[1] ACR (American College of Rheumatology) responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a ≥20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥20% improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.

[2] TGA, AusPAR for tocilizumab, January 2011. Available at: http://www.tga.gov.au/pdf/auspar/auspar-actemra.pdf

Systemic idiopathic juvenile arthritis (sJIA) is a subtype of juvenile idiopathic arthritis characterised by systemic manifestations of disease in addition to arthritis.[3] It occurs at all ages with some predilection for children less than 5 years of age. Currently JIA is diagnosed with a minimum disease duration of 6 weeks. There are no pathognomonic features for sJIA but diagnosis is usually made after 2 weeks of daily high fever spikes, transient rash, importantly development of arthritis may lag behind by months. Other manifestations of disease are hepatosplenomegaly, lymphadenopathy and serositis. sJIA accounts for 10-20% of all JIA cases.[3] Important complications of the disease are disability, osteoporosis, growth retardation, secondary amyloidosis and anaemia. A life threatening complication occurring in about 5% of cases is the so-called macrophage activation syndrome (MAS) which is an overwhelming systemic inflammatory reaction.[3]About 50% of patients develop an unremitting course; about a quarter of patients develop severe arthritis with significant disability.[3]

This AusPAR describes the evaluation of an application by Roche Products Pty Ltd (the sponsor) for a further extension of indications to include patients with systemic juvenile idiopathic arthritis (sJIA). The proposed indication is:

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

Regulatory Status

The product received initial ARTG Registration in May 2009.

The extension of indications to include sJIA has been approved in the European Union (EU) (1 August 2011), the USA (15 April 2011) and Switzerland (28 June 2011). The relevant approved specific indications in the EU and the USA are as follows:

Europe

RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

USA

Actemra (tocilizumab) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

The submission is still under evaluation in Canada and has yet to be submitted in New Zealand.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

[3] EMA. Assessment Report for RoActemra (EPAR), August 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000955/WC500111086.pdf

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

This submission proposed an extension of indication of Actemra (tocilizumab) from adult rheumatoid arthritis (RA) to children aged 2-18 years with systemic juvenile idiopathic arthritis (sJIA).

Tocilizumab is a recombinant, humanised IgG1 monoclonal antibody that binds to the human interleukin-6 receptor (IL-6R) blocking the detrimental effects associated with over expression of IL-6 in RA.

Nonclinical efficacy studies were not submitted and were not considered necessary in light of the clinical trial data showing efficacy in children with sJIA.

Nonclinical safety studies were conducted in order to support the newly intended clinical population spanning 2-18 years of age. However, due to the species specificity of tocilizumab to humans and monkeys, mouse studies were performed using MR16-1, a rat-anti-mouse IL-6R monoclonal antibody (IgG) which was previously characterised as a suitable rodent analog of tocilizumab.

New nonclinical safety data in the current submission consisted of Good Laboratory Practice (GLP) compliant developmental toxicity studies in juvenile mice receiving MR16-1 (murine analog of tocilizumab) by intravenous (IV) infusion. These studies bridged the gap between the previously evaluated pre/postnatal studies with MR16-1 in mice and previously evaluated studies with tocilizumab in adolescent and adult monkeys. Moreover, the new studies included the assessment of the effects of MR16-1 on both immunophenotype and immunocompetence.

Toxicokinetics

Toxicokinetic data showed that the dosing schedule of IV infusion of 15 or 50 mg/kg MR16-1 every three days in mice achieved steady state levels over the treatment period from weaning (Post Natal Day [PND]22) to sexual maturity (PND 79). MR16-1 was cleared from the circulation by 50 days after the last dose. Unlike previous studies, there was no evidence of reduced exposure due to anti-MR16-1 antibody formation, probably due to the 50 mg/kg loading dose given in this protocol.

Toxicology

Developmental toxicity

General

No mortality or abnormalities in clinical signs or body weight were observed in the juvenile mouse toxicity study. Crown to rump length and femur and humerus lengths were no different between treated and control animals and there were no skeletal abnormalities. Sexual maturation and oestrus cycles were no different between treated and control animals. Previously submitted data on the effects of MR16-1 on postnatal development of pups after dosing of dams at 0, 15 or 50 mg/kg every 3 days from Gestation Day (GD)6 to PND21 showed no effects on clinical signs, external features, body

weight, functional or physical development, external, visceral or skeletal findings, external genitalia, open field test, learning or reproductive ability.

There was a slight increase in abnormal sperm after dosing and recovery in the 50 mg/kg group; small increases in abnormal sperm (3-4%) were found in a previously evaluated study in adult rats treated with 16 and 50 mg/kg/day.

There were dose related decreases in monocyte counts in males and females but no significant decreases in neutrophils or platelets as has been observed in clinical trials of tocilizumab in children. Males and females showed dose related reduction in serum glucose, increase in globulin and α2-globulin and decrease in β-globulin and the A/G ratio was lower in 50 mg/kg group. After the recovery period, monocyte counts normalised, α2-globulin was lower and the A/G ratio was higher in males.

Dose related increases in thyroid weights in males at the end of the dosing period were reversed in the recovery period. Minor histopathology findings in control and treated animals did not appear to be treatment related.

Central nervous system (CNS) effects

No tests of learning and memory were conducted in the new developmental toxicity studies. Such tests might have shed light on the role of IL-6 in these processes during development. The published literature on IL-6 and memory in rodents is complex and conflicting, with evidence for both protective and detrimental roles for IL-6 (Adler, 2007; Hryniewicz *et al*. 2007: Baier *et al*. 2009; Yirmiya and Goshen, 2011).[4,5,6,7] Regardless, tocilizumab may only affect central IL-6 signalling if it can cross the brood brain barrier (BBB), which normally prevents entry of antibodies (Lampson, 2011).[8] Tissue distribution data from the primary evaluation of Actemra showed low levels of radioactivity in the brain of rats and monkeys but it was unclear whether this represented ^{125}I-tocilizumab or free ^{125}I.

Developmental immunotoxicity

Small but significant effects were seen in T cell subsets in peripheral blood during the dosing period and after the recovery period (decreased CD3e+CD4+CD8a and CD49b/Pan-NK cells+CD3e−, CD3e+ ; increased CD45R/B220+) with minor effects in T cell subsets in spleen (increased CD45R/B220+ in females) and thymus (decreased CD4-CD8a- in males). The effects on T cell subsets were small but sustained up to 50 days after the end of treatment; this suggests that IL-6 blockade during development may have long term effects on immune parameters. However, these subset changes did not result in any functional impairment of the immune system as shown by a lack of effect of MR16-1 on NK cell activity or on the capacity of the immune system to mount an immunoglobulin G (IgG) or immunoglobulin M (IgM) mediated immunisation response.

Overall, the present immunotoxicity results are similar to those seen in a previously evaluated postnatal rat study and confirm that there are no adverse effects of MR16-1 on immunocompetence, despite small but significant changes in lymphocyte subsets.

[4] Adler, R (ed.) 2007, Pyschoneuroimmunology, Vol 1, Elsevier, London.

[5] Hryniewicz A, Bialuk I, Kamiński KA, Winnicka MM. Impairment of recognition memory in interleukin-6 knock-out mice. Eur J Pharmacol 2007; 577: 219-20.

[6] Baier PC, May U, Scheller J, Rose-John S, Schiffelholz T. Impaired hippocampus-dependent and -independent learning in IL-6 deficient mice. Behav Brain Re 2009; 200: 192-6.

[7] Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav Immun 2011; 25: 181-213.

[8] Lampson LA. Monoclonal antibodies in neuro-oncology: Getting past the blood-brain barrier. MAbs 2010; 3: (2).

Immunogenicity

Tocilizumab is a humanised monoclonal antibody which may be recognised as foreign in animal studies and elicit an immune response. For this reason, the predictive value of non-clinical studies for evaluation of immunogenicity in biological products is considered low.[9]

Anti- MR16-1 antibody analysis conducted in the juvenile mouse studies showed the formation of antibodies at a low titre in some animals at the end of the dosing period and during the recovery period. However, as MR16-1 is a rat IgG1 monoclonal antibody with specificity for mouse IL-6 receptor, it may be recognised as foreign in mice eliciting an immune response. The value of immunogenicity studies in this context is to ensure that antibody effects do not limit exposure and invalidate safety studies. The data confirm that there were no significant antibody related effects on exposure.

Nonclinical Summary and Conclusions

Nonclinical efficacy studies were not submitted and were not considered necessary in light of the clinical trial data.

New GLP compliant developmental toxicity studies were conducted in juvenile mice, which were treated IV from PND 22 to PND 79 with the murine analog of tocilizumab, MR16-1. These studies bridged the gap between the previously evaluated pre/postnatal studies with MR16-1 in mice and previously evaluated studies with tocilizumab in adolescent and adult monkeys.

New toxicokinetic data and previous pharmacodynamic data showed that the dosing schedule of IV infusion of 15 or 50 mg/kg MR16-1 every three days in mice achieved steady state levels and maximal pharmacological efficacy over the treatment period from weaning to sexual maturity. There was no evidence of reduced exposure due to anti-MR16-1 antibody formation. MR16-1 was cleared from the circulation by 50 days after the last dose.

General toxicity observations were limited to decreased monocyte counts; minor effects on changes in serum glucose and globulins; and increased thyroid weights in males. These effects were partially or fully reversible and were not toxicologically significant. There was no significant suppression of neutrophils and platelets or elevation in hepatic transaminases as has been observed in clinical trials of tocilizumab in children.

Sexual maturation and skeletal development (as shown by morphological differentiation of external genitalia, oestrus cycle, sperm examination, crown rump length, skeletal abnormalities) were unaffected by MR16-1.

Immunophenotyping showed small but significant changes in lymphocyte subsets after MR16-1 treatment. However, these changes did not result in any functional impairment of the immune system as shown by a lack of effect of MR16-1 on NK cell activity or on the capacity of the immune system to mount an IgG or IgM mediated immunization response.

No tests of learning and memory were conducted in the new developmental toxicity studies.

There were no meaningful, treatment related adverse effects of MR16-1 on postnatal growth/development and sexual maturation in juvenile animals. The small changes in lymphocyte subsets were not associated with a decline in immunocompetence.

[9]EMEA, Committee for Medicinal Products for Human use (CHMP), 13 December 2007. Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins. EMEA/CHMP/BMWP/14327/2006.

Overall, the results from studies using the murine analogue of tocilizumab suggest no major concerns regarding the possible effects of blocking IL-6 action on postnatal growth and development.

The effects of tocilizumab on the immune system and increased susceptibility to infection are evident from the clinical data and no additional effects have been identified in the nonclinical studies. Moreover, the significance of any minor changes noted in the animal toxicity studies should be outweighed by any observed clinical reductions in morbidity, mortality or long term articular complications (such as abnormal growth and sexual maturation) following tocilizumab treatment of patients aged 2 to 18 years of age.

There were no nonclinical objections to the registration of tocilizumab for the proposed extension of indication.

IV. Clinical Findings

Introduction

This application for extension of indication in sJIA was supported by data from the pivotal study WA18221 (the TENDER study) and a number of supportive studies.

Pharmacokinetics

Introduction

The pharmacokinetic data were from a population pharmacokinetic study conducted as part of a larger study, Study WA18221.

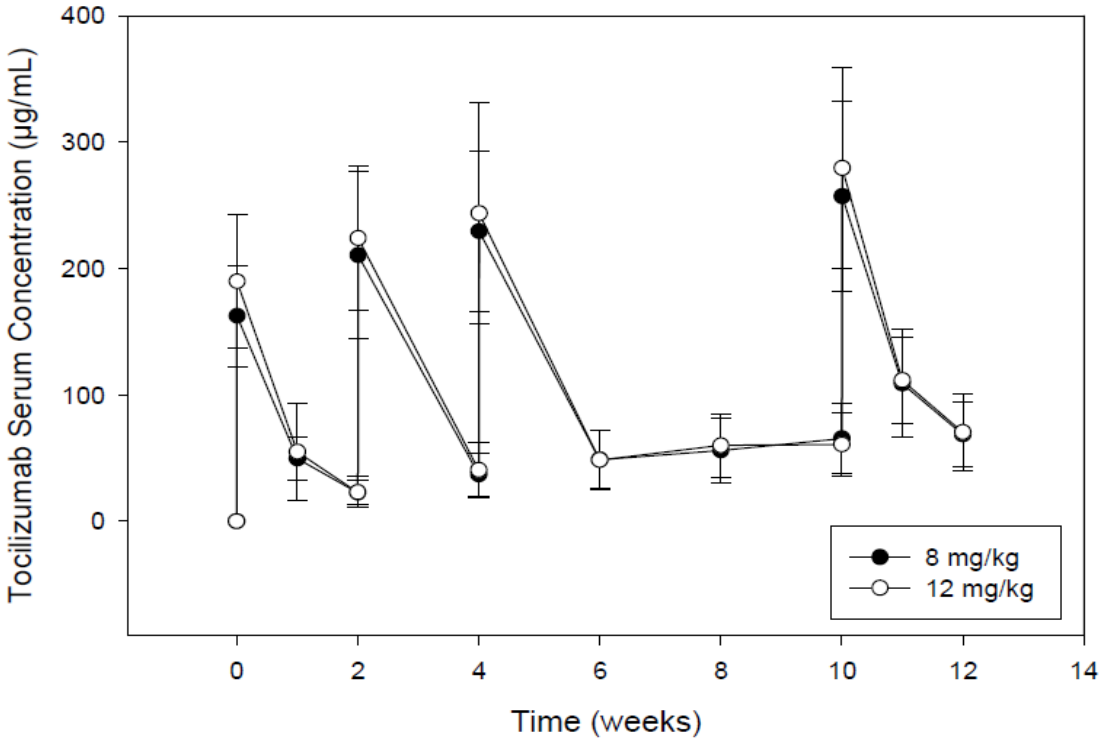
Data submitted in support of pharmacokinetics

Study WA18221 was a 12 week randomized, double blind, placebo controlled, parallel group, two arm study to evaluate the efficacy and safety of tocilizumab (TCZ) in patients with active sJIA; with a 92 week single arm open label extension, followed by a 3 year open label continuation.

There were 112 subjects included in the study: 75 received TCZ for 12 weeks; 37 received TCZ 8 mg/kg and 38 received TCZ 12 mg/kg. All subjects who received TCZ provided at least one quantifiable TCZ concentration and were included in the pharmacokinetic (PK) analysis.

There were a total of 859 samples from 75 patients. Mean serum concentrations of TCZ are plotted in Figure 1. There were similar PK parameters for the 8 mg/kg and 12 mg/kg groups. The area under the serum concentration time curve (AUC) was not strongly associated with body weight or body surface area (BSA). Mean (standard deviation [SD]) model predicted AUC over two weeks (AUC_{2weeks}), minimum (trough) serum concentration (C_{min}) and maximum serum concentration (C_{max}) were: 1341.332 (414.332) µg•day/mL; 57.523 (23.3427) µg/mL and 244.762 (57.1606) µg/mL respectively. This corresponds with a mean (SD) model predicted AUC_{2weeks} of 32191.968 (9943.968) µg•hr/mL. There was a threefold increase in mean TCZ pre-dose concentrations between Week 2 and 12: mean (SD) Week 2 pre-dose concentrations 22.8 (10.9) µg/mL; and 69.5 (27.7) µg/mL at Week 12. Hence the accumulation ratio for this time period was 3.1.

Figure 1: Mean (± SD) serum TCZ concentration time profile by treatment group (N=37 at 8 mg/kg and N=38 at 12 mg/kg)



Evaluator's overall conclusions on pharmacokinetics

The population pharmacokinetic study was not reported in sufficient detail to enable appraisal of the methodology and there was incomplete reporting of the pharmacokinetic parameters. Clearance, volume of distribution and $t_{1/2}$ were not reported. The sponsor should submit a comprehensive report of the population pharmacokinetic analysis.

Pharmacodynamics

Introduction

There were some pharmacodynamic data reported in Study WA18221.

Data submitted in support of pharmacodynamics

In Study WA18221, serum samples were analysed for serum interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R) using ELISA methods. Concentrations of both IL-6 and sIL-6R increased relative to placebo during the 12 week treatment period. There were no significant differences between the treatment groups in absolute C-telopeptide or osteocalcin, but N-terminal propeptide (PINP) was higher in the TCZ groups at Week 12: mean (SD) 428.25 (278.778) ng/mL for TCZ and 281.65 (209.877) ng/mL for placebo. IL-17 concentrations were higher in the TCZ group at baseline and Week 12. C3 and C4 concentrations decreased in the TCZ group to Week 12, but there was no apparent change in the placebo group. There was similar exposure to TCZ in the responder and nonresponder groups.

Evaluator's overall conclusions on pharmacodynamics

The increases in serum concentrations of IL-6 and sIL-6R are consistent with the proposed mechanism of action of TCZ. Response to TCZ did not appear to be related to the magnitude of TCZ exposure. Hence there would be no benefit in monitoring serum TCZ concentrations.

Efficacy

Introduction

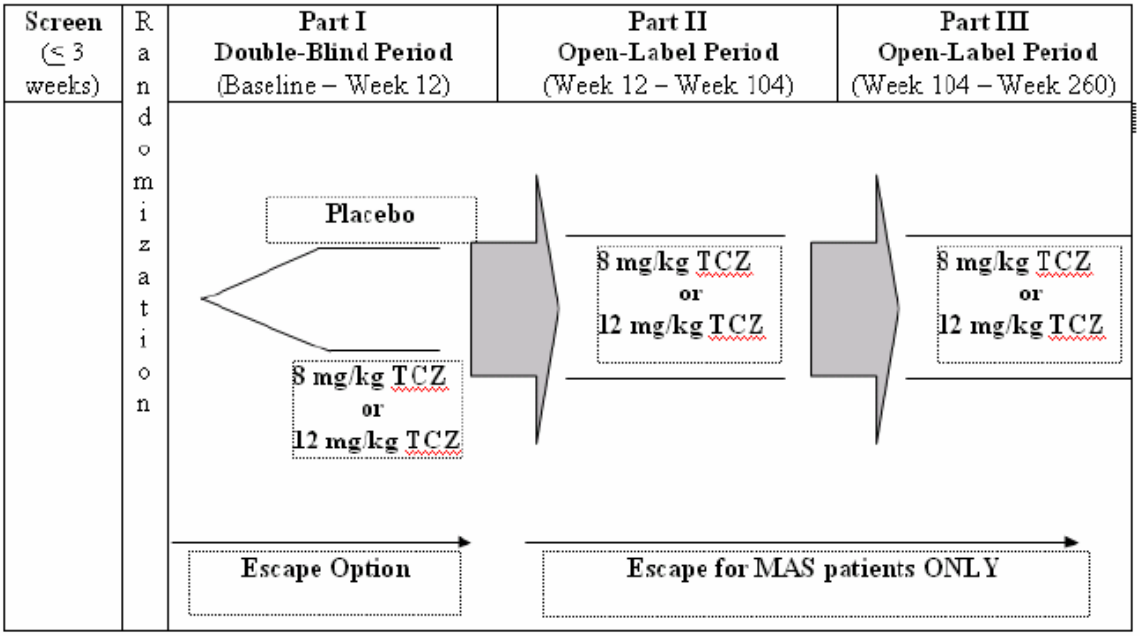
Efficacy data were presented from one placebo controlled study of 12 weeks duration (Study WA18221) and one combined long term, open label follow up study (Study MRA317JP/MRA324JP)

Efficacy data from controlled studies

Methods for Study WA18221

Study WA18221 was a 12 week randomized, double blind, placebo controlled, parallel group, two arm study to evaluate the efficacy and safety of tocilizumab (TCZ) in patients with active sJIA; with a 92 week single arm open label extension, followed by a 3 year open label continuation. The overall study plan is summarized in Figure 2. The study was conducted at 43 centers in 17 countries. Only the data from the 12 week randomized double blind phase were included in the study report.

Figure 2: Overview of study design



The inclusion criteria included:

Patients with sJIA (from age 2 years onward at screening) as classified by the International League of Associations for Rheumatology (ILAR) criteria and symptoms of persistent disease for at least 6 months with inadequate response to nonsteroidal antiinflammatory drugs (NSAIDs) and systemic corticosteroids (CSs) due to toxicity or lack of efficacy

- Children age 2 years up to and including age 17 years with active sJIA
- Documented sJIA disease duration of ≥6 months
- ≥5 active joints or ≥2 active joints with fever > 38° C for any 5 out of 14 days during screening
- Patients taking NSAIDs, CSs or MTX were permitted but had to enter the study on a stable dose of these medications
- Patients had to have active arthritis at screening

The treatment groups were:

1. TCZ
2. placebo

Subjects were randomised to TCZ:placebo in a 2:1 ratio. For Part 1, the treatments were administered as infusions every two weeks over 12 weeks. The TCZ dose was either 8 mg/kg for patients ≥30 kg or 12 mg/kg for patients < 30 kg. Randomisation to TCZ was stratified by weight group in a 1:1 ratio. There were six infusions in total. The open label phases of the trial were: Part 2 (92 weeks duration) and Part 3 (3 years duration).

The primary efficacy outcome measure was the proportion of subjects with at least 30% improvement in JIA ACR core set (JIA ACR30 response) at Week 12 and absence of fever (defined as no diary temperature recording ≥37.5° C in the preceding seven days). The secondary efficacy outcome measures were:

- The proportion of subjects with fever due to sJIA at baseline who are free of fever at Week 12
- The proportion of subjects with JIA ACR30 response at Week 12
- The proportion of subjects with JIA ACR50 response at Week 12
- The proportion of subjects with an elevated C-reactive protein (CRP) at baseline who have normal CRP at Week 12
- The percentage change from baseline (CFB) in erythrocyte sedimentation rate (ESR) at Week 12
- The percentage CFB in the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) score at Week 12
- The proportion of subjects with JIA ACR70 response at Week 12
- The percentage CFB in physician's global assessment of disease activity visual analogue scale (VAS) at Week 12
- The percentage CFB in parent/patient's global assessment of overall wellbeing VAS at Week 12
- The proportion of subjects with anaemia at baseline who increase haemoglobin (Hb) by ≥10 g/L at Week 12
- The proportion of subjects with anaemia at baseline who increase Hb by ≥10 g/L at Week 6
- The proportion of subjects with rash characteristic of sJIA at baseline who are free of rash at Week 12
- The CFB in the pain VAS at Week 12
- The proportion of subjects with a minimally important improvement in the CHAQ-DI by Week 12
- The proportion of subjects with JIA ACR30 response at Week 12 adjusted for oral CS dose modifications
- The proportion of subjects receiving oral CSs with a JIA ACR70 response at Week 6 or Week 8 who then reduce their oral CS dose by at least 20% without subsequent JIA ACR30 flare or occurrence of systemic symptoms to Week 12
- The proportion of subjects with JIA ACR90 response at Week 12
- The proportion of subjects with thrombocytosis at baseline who have a normal platelet count at Week 12
- The proportion of subjects with leucocytosis at baseline who have a normal total white blood cell (WBC) count at Week 12
- The proportion of subjects with anaemia at baseline who have normal Hb at Week 12
- The percentage CFB in number of joints with active arthritis at Week 12
- The percentage CFB in number of joints with limitation of movement at Week 12

- Childhood Health Assessment Questionnaire (CHAQ) and Childhood Health Assessment Questionnaire (CHQ-PF50)

Primary PK parameters such as clearance and volume of distribution were estimated from the sparse sampling dose concentration time data of TCZ using population PK methods.[10] Secondary PK parameters such as AUC were derived from the individual *post hoc* predictions. The relationship between TCZ exposure and efficacy and safety parameters (for example, JIA core set score and infections) were explored. Safety was assessed using reporting of adverse events (AEs), clinical laboratory results, and physical examinations including vital signs and electrocardiograms. Previous and concomitant medications and procedures were recorded. Purified Protein Derivative (PPD) test and chest X-rays were obtained prior to randomization.

Statistical considerations

Hypothesis tests for the primary endpoint were performed using the Cochran-Mantel-Haenszel (CMH) test. Logistic regression analysis was used in confirmatory exploratory analyses. Analysis of variance (ANOVA) was used to test the change from baseline endpoints. The models included the stratification factors applied at randomization: weight, duration of disease, background oral CS dose and background MTX use. In subjects remaining in the study to Week 12, missing data was imputed using the last observation carried forward (LOCF) methodology.

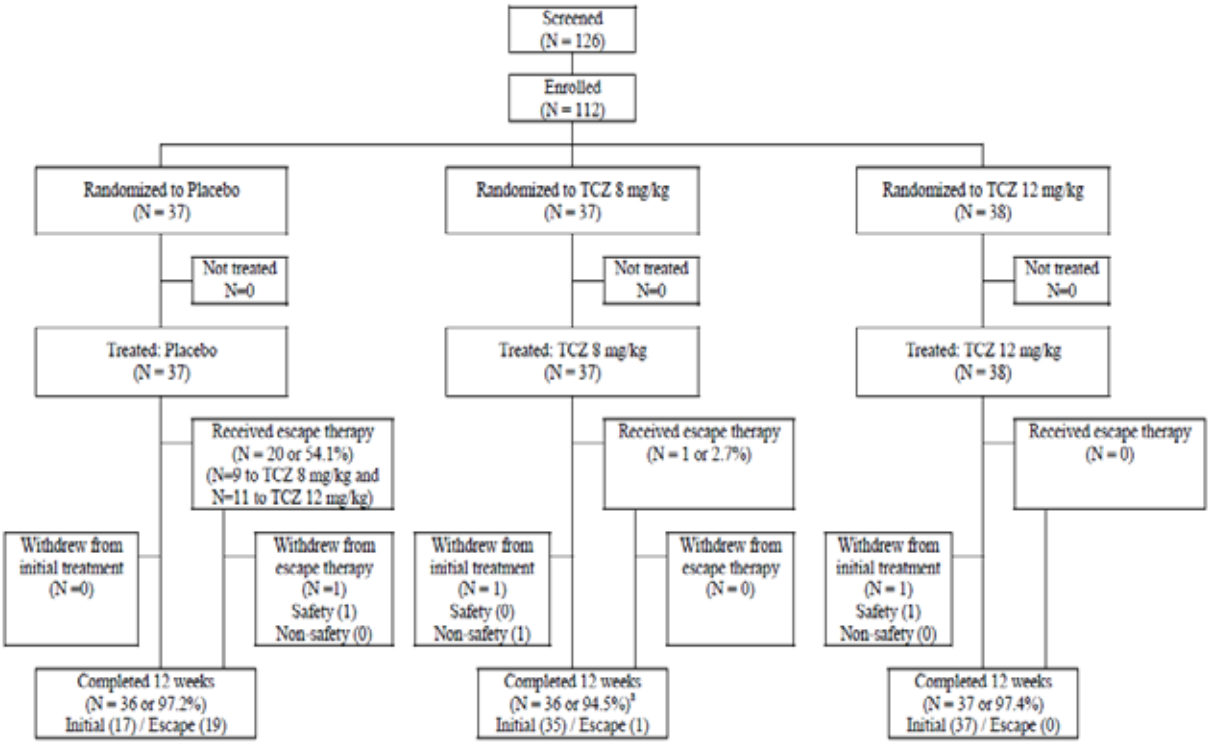
Based on the reported literature of previous studies, it was assumed that the JIA ACR30 response at Week 12 would be 70% for patients on TCZ and 40% for patients on placebo treatment. Patients who withdrew, received escape therapy or for whom the endpoint could not be determined would be classified as JIA ACR30 nonresponders. The sample size was calculated to be 72 patients in the combined TCZ group and 36 patients in order to provide 80% power to detect a significant treatment difference using a two-sided significance test with α=0.05.

Results for Study WA18221

A total of 126 subjects were screened and 112 were randomized to treatment: 37 to TCZ 8 mg/kg, 38 to 12 mg/kg and 37 to placebo. All randomised subjects received treatment and were included in the "intention to treat" (ITT) analysis (Figure 3). A total of 36 (94.5%) subjects in the 8 mg/kg group, 37 (97.4%) in the 12 mg/kg and 36 (97.2%) in the placebo completed the study. There were 56 (50%) males, 56 (50%) females and the age range was 2 to 17 years. The treatment groups were similar in demographic characteristics, except for the expected differences in size between the TCZ 8 mg/kg and 12 mg/kg groups. The treatment groups were slightly different in baseline disease characteristics but in the efficacy analysis this would have been accounted for by the use of a change from baseline analysis. The treatment groups were similar in JIA ACR core components at baseline. A total of 26 (70%) subjects in the placebo group and 52 (69%) in the TCZ were being treated with MTX at baseline.

[10] "Sparse" refers to a technique employed in population pharmacokinetic studies where a small number of samples are obtained from a large number of subjects.

Figure 3: Patient disposition



Percentages based on the number of treated patients in each group.

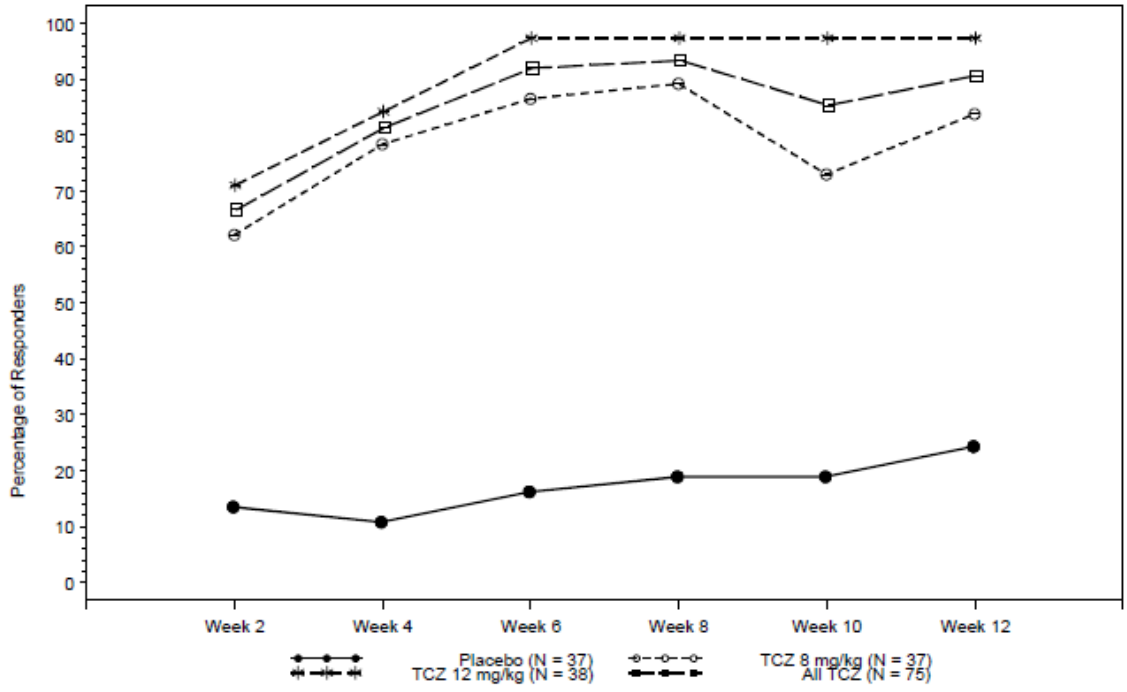
For the primary efficacy outcome variable, there was a higher proportion of responders in the combined TCZ group than the placebo group, p <0.0001 (Table 1). The number (%) of responders was nine (24.3%) subjects for placebo, 28 (75.7%) for TCZ 8 mg/kg, 36 (94.7%) for TCZ 12 mg/kg and 64 (85.3%) for the TCZ combined group. There were similar findings for ACR30, ACR50, ACR70 and ACR90. The ACR50 response occurred for four (10.8%) subjects in the placebo group, 29 (78.4%) in the TCZ 8 mg/kg, 35 (92.1%) in the TCZ 12 mg/kg and 64 (85.3%) in the TCZ combined group. Maximum JIA ACR response occurred by Week 6 and was maintained to Week 12 (Figure 4). Improvement was demonstrated for each of the JIA ACR core set components. There was a reduction in the number of joints with active arthritis in all the treatments groups, with the greatest reduction in the 12 mg/kg group. There was a reduction in the number of joints with limitation of movement in all the treatments groups, with the greatest reduction in the 12 mg/kg group. In the TCZ groups there were higher proportions of subjects receiving oral CSs with a JIA ACR70 response at Week 6 or Week 8 who then reduced their oral CS dose by at least 20% without subsequent JIA ACR30 flare or occurrence of systemic symptoms to Week 12: one (3.2%) subject in the placebo group, eight (23.5%) in the 8 mg/kg, nine (25.0%) in the 12 mg/kg and 17 (24.3%) in the combined TCZ.

Table 1: Summary and analysis of the percentage of patients with a JIA ACR30 response and absence of fever at Week 12 (ITT population)

	Placebo (N=37)	TCZ 8 mg/kg (N=37)	TCZ 12 mg/kg (N=38)	All TCZ (N=75)
n	37	37	38	75
Responders	9 (24.3%)	28 (75.7%)	36 (94.7%)	64 (85.3%)
95% C.I.	[10.5; 38.1]	[61.9; 89.5]	[87.6;100.0]	[77.3; 93.3]
Weighted difference vs. Placebo				61.5
95% C.I. of weighted difference				[44.9; 78.1]
p-value				<.0001

Responders are patients who had a JIA ACR30 response at Week 12 and absence of fever (temperatures <37.5C) in the 7 days preceding the Week 12 assessment day.
Patients who withdrew, received escape medication, or for whom the endpoint could not be determined are classified as non-responders.
LOCF rule applied to missing JIA ACR core set components at Week 12.
Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at Baseline.
Treatment comparisons are vs. Placebo.
C.I. = Confidence Interval.

Figure 4: Line plot of the proportion of JIA ACR30 responders by visit To Week 12 (ITT Population)



At each timepoint responders are patients who had a JIA ACR30 response.
Patients who withdrew, received escape medication, or for whom the endpoint could not be determined are classified as non-responders.
LOCF rule applied to missing JIA ACR core set components at visits.

The logistic regression analysis of ACR30 response indicated a significant effect for MTX use, with a reduction in the odds of response associated with MTX use: OR (95% confidence intervals [CI]) 0.23 (0.05 to 0.94) p=0.0414. The effect size might in reality be greater due to confounding by more subjects in the higher dose group being treated with MTX: 21 (57%) subjects in the 8 mg/kg group and 31 (82%) in the 12 mg/kg. When adjusted for oral corticosteroid dose modification, the treatment effect was still greater in the combined TCZ group compared to placebo.

The proportion of subjects free of fever was greater in the TCZ groups: five (20.8%) subjects in the placebo group, eleven (73.3%) in the 8 mg/kg, 24 (92.3%) in the 12 mg/kg and 35 (85.4%) in the combined TCZ group. The proportion of subjects with rash at baseline becoming free of rash by Week 12 was greater in the TCZ groups: two (11.1%) subjects in the placebo group, four (44.4%) in the 8 mg/kg, ten (76.9%) in the 12 mg/kg and 14 (63.6%) in the combined TCZ group. VAS for pain decreased to a greater extent in the combined TCZ group compared with placebo: adjusted mean difference -39.8 (-55.1 to -24.6), p <0.0001.

The percentage of subjects with elevated CRP at baseline that subsequently normalized was: two (5.9%) for placebo, 35 (100.0%) for 8 mg/kg, 36 (97.3%) for 12 mg/kg and 71 (98.6%) for combined TCZ. The proportion of subjects with anaemia at baseline who have normal Hb at Week 12 was higher in the TCZ groups: two (6.9%) subjects in the placebo group, 20 (83.3%) in the TCZ 8 mg/kg, 20 (76.9%) in the 12 mg/kg and 40 (80.0%) in the combined TCZ. The percentage of subjects with anaemia at baseline and increase in Hb ≥10 g/L at Week 12 was one (3.4%) subject in the placebo group, 22 (91.7%) in the 8 mg/kg, 22 (84.6%) in the 12 mg/kg and 44 (88.0%) in the combined TCZ group. The proportion of subjects with thrombocytosis at baseline who have a normal platelet count at Week 12 was one (3.8%) in the placebo group, 22 (91.7%) in the 8 mg/kg, 25 (89.3%) in the 12 mg/kg and 47 (90.4%) in the combined TCZ group. The proportion of subjects with leucocytosis at baseline who have a normal total WBC count at Week 12 was two (9.5%) subjects in the placebo group, eight (72.7%) in the 8 mg/kg, 13 (76.5%) in the 12 mg/kg and 21 (75.0%) in the combined TCZ group. There were improvements in CHQ-PF50 physical and psychosocial scores in the TCZ groups compared to placebo but the statistical significance was not reported.

However, despite the logistic regression analysis suggesting an effect for MTX in reducing response, there did not appear to be a clinically significant difference in efficacy between those subjects treated with MTX at baseline and those not.

When analysed by age category (2 to 5 years, 6 to 12 years and 13 to 18 years) there was similar efficacy for each of the age groupings.

Long term efficacy data

Methods for Study MRA317JP/MRA324JP

Study MRA317JP/MRA324JP was a combined report of long term follow up data from Studies MRA011JP, MRA317JP, MRA316JP and MRA324JP. The studies were all sponsored by Chugai Pharmaceutical Co. Ltd and conducted in Japan. The studies all included subjects with JIA based on ILAR criteria. All of the studies used as the study treatment: TCZ 8 mg/kg every 2 weeks. The TCZ was presented in a 200 mg for infusion formulation.

During treatment with TCZ the following concomitant treatments were prohibited:

- DMARDs or immunosuppressants (for example, methotrexate, infliximab, etanercept, leflunomide, cyclosporine, sodium aurothiomalate, auranofin, D-penicillamine, lobenzarit, bucillamine, actarit, salazosulfapyridine, mizoribine and azathioprine)
- Intra-articular injection of hyaluronate preparations
- Plasmapheresis
- Other investigational products
- Other drugs and therapies that may affect evaluation of drug efficacy

The following concomitant treatments were allowed:

- Oral corticosteroids
- Topical corticosteroids

- NSAIDs
- Intravenous, intramuscular or intra-articular administration of corticosteroids were permitted, but were to be avoided as long as it was possible
- Surgical procedure (operation, etc.)
- Other drugs for the treatment of concurrent disease believed to have no effect on evaluation of drug efficacy

The primary efficacy outcome measure was the percentage of patients showing 30% improvement in the JIA core set on the last observation day. The secondary efficacy outcome measures were:

- Time courses of CRP and ESR
- Time course of percentage of patients showing 30%, 50% and 70% improvement in the JIA core set
- Time courses of individual JIA core set components
- Time course of pain (VAS)
- Time course of corticosteroid dose

The time course for these outcome measures was from before the first infusion of the investigational product, including the previous study.

Results for Study MRA317JP/MRA324JP

Across all of the studies there were 149 subjects enrolled and treated (Figure 5). A total of 67 subjects were enrolled in StudyMRA011JP/MRA316JP, all received study treatment; 60 subsequently enrolled in Study MRA317JP and 58 completed. There were nine subjects withdrawn from StudyMRA011JP/MRA316JP/317JP: four because of AEs and four because of the development of antibodies. A total of 82 subjects were enrolled in Study MRA324JP, all received treatment and 74 completed the study (Figure 6). Eight subjects withdrew from MRA324JP: three due to the occurrence of anti-MRA antibodies; four because of AE. There were 80 (54.1%) females, 68 (45.9%) males and the age range was 2 to 34 years. There were 123 (82.6%) subjects aged less than 15 years, including 49 (33.1%) aged less than 7 years.

Figure 5: Patient disposition—MRA011JP/MRA316JP/MRA317JP

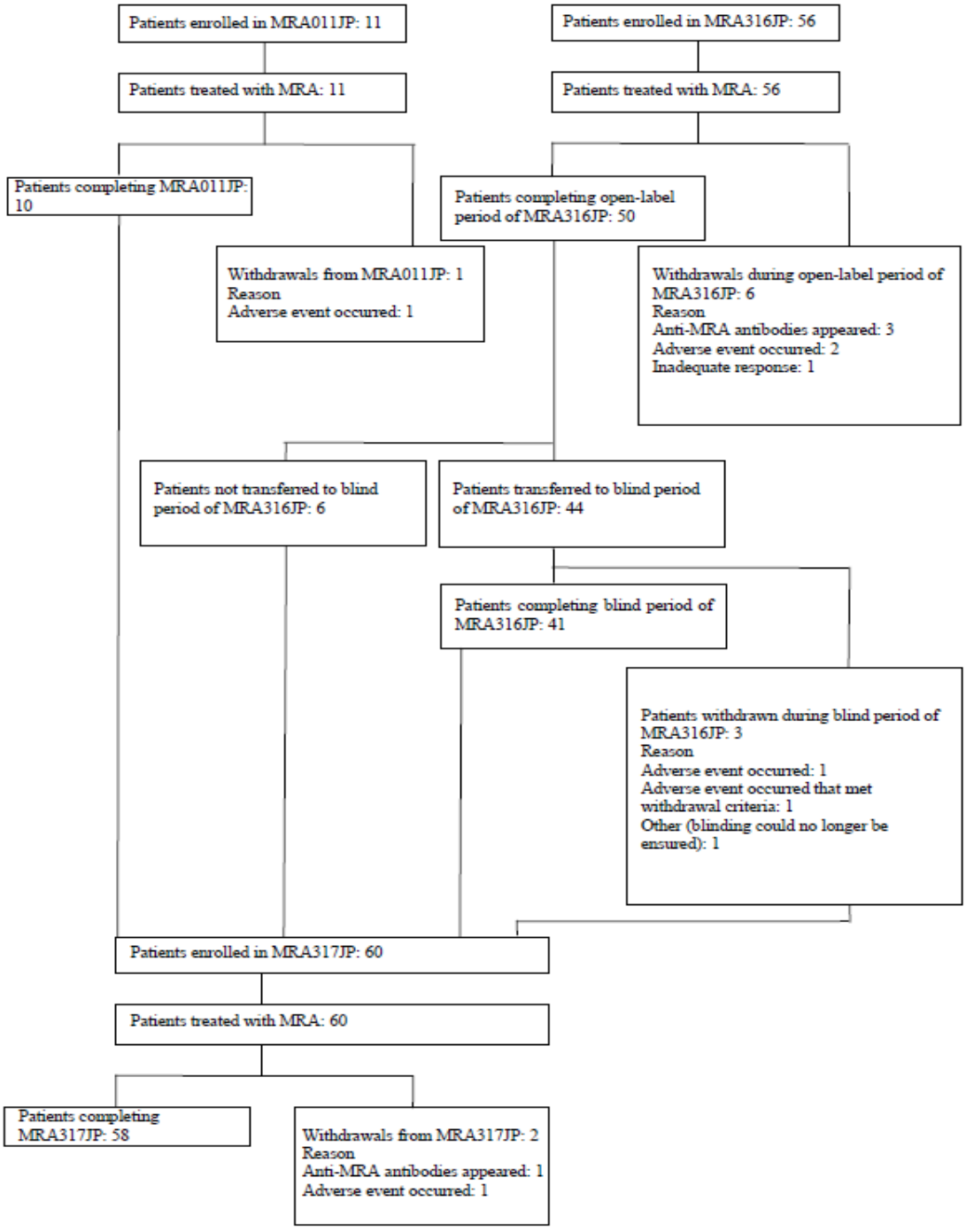
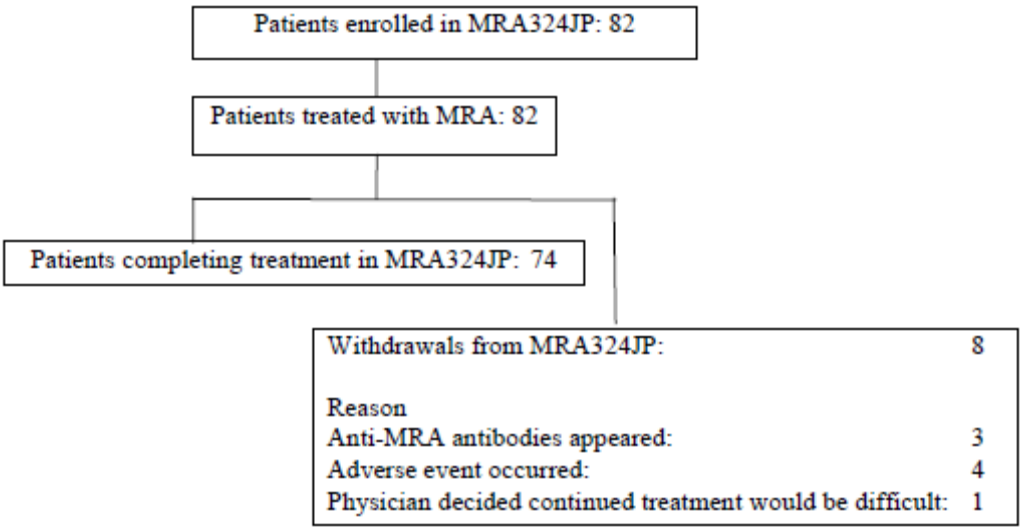


Figure 6: Patient disposition—MRA324JP

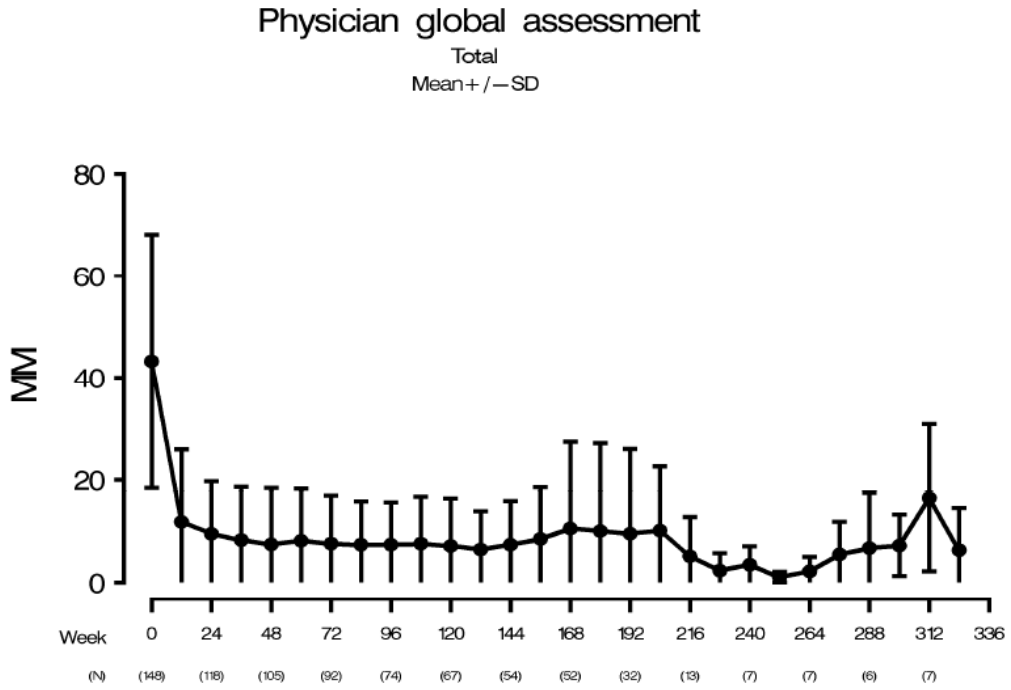


For those subjects that remained in the study, response rates were maintained for up to 324 weeks. The improvements were maintained in:

- Physician global assessment (Figure 7)
- Parent/patient global assessment
- CHAQ
- Number of active joints
- Number of joints with limited range of movement
- ESR
- CRP
- VAS of pain
- Average daily corticosteroid dose

Serum IL-6 concentrations increased to Week 24, then remained stable. The trough serum myeloma receptor antibody (tocilizumab) (MRA) concentration was mostly in the range 10 to 100 µg/mL. Improvement in joint symptoms and normalization of CRP was seen when serum MRA concentration was maintained at a level of at least 1 µg/mL.

Figure 7: Time course of mean values for physician global assessment



Evaluator's overall conclusions on clinical efficacy

Study WA18221 demonstrated efficacy for TCZ in children and adolescents with sJIA over a 12 week period. The treatment effect was clinically significant to the extent that the study subjects had marked improvement in all of the study measures. There was no apparent difference in efficacy between subjects treated with MTX and those who were not. CS dose did not appear to influence efficacy. Efficacy was not influenced by age group.

Study MRA317JP/MRA324JP indicated that efficacy persisted for up to 324 weeks. However, because the study was not placebo controlled it is not clear to what extent the response rate might have been influenced by the natural history of sJIA, that is, the proportion of subjects that might have undergone spontaneous remission. It is also not clear how many subjects might have been treated with MTX and how this might have influenced the treatment effect.

Safety

Introduction

Safety data were presented from the two studies discussed above, Study WA18221 and Study MRA317JP/MRA324JP. Other than these two studies, there were no additional safety data included in the submission.

Patient exposure

In Study WA18221 Part 1, exposure to study medication was a median of 12.14 weeks for both TCZ dose levels (8 mg/kg and 12 mg/kg) (Table 2). A total of 75 subjects were exposed to TCZ for a total of 897 patient weeks. There were 16 subjects aged 2 to 5 years, 33 subjects aged 6 to 12 years and 26 aged 13 to 18 years.

Table 2: Summary of duration in study and exposure to trial treatment at Week 12 by trial treatment (safety population)

	Placebo N = 37	TCZ 8 mg/kg N = 37	TCZ 12 mg/kg N = 38	All TCZ N = 75
Duration in Study (Weeks)				
Mean	7.37	11.98	12.24	12.11
SD	4.893	1.314	0.303	0.950
SEM	0.804	0.216	0.049	0.110
Median	8.00	12.14	12.14	12.14
Min-Max	0.3 - 13.0	4.3 - 13.0	11.7 - 13.0	4.3 - 13.0
Sum	272.7	443.1	465.0	908.1
n	37	37	38	75
Exposure to Trial Treatment (Weeks)				
Mean	7.52	11.91	12.01	11.96
SD	4.699	1.310	0.486	0.978
SEM	0.772	0.215	0.079	0.113
Median	8.43	12.14	12.14	12.14
Min-Max	2.1 - 13.0	4.4 - 12.4	10.1 - 12.6	4.4 - 12.6
Sum	278.3	440.6	456.4	897.0
n	37	37	38	75

n represents number of patients contributing to summary statistics.
Duration in study (weeks) = (date of last assessment - date of first dose + 1) / 7.
Exposure to trial treatment (weeks) = (date of last dose - date of first dose + 15) / 7.
Sum is across all patients in the treatment arm.
Data on escape therapy is excluded.

For Study MRA317JP/MRA324JP, 149 subjects were exposed to TCZ for a median (range) duration of 2.111 (0.04–6.22) years, and the mean (SD) dose per two weeks was 7.408 (1.258) mg/kg. Exposure to TCZ is summarized in Table 3.

Table 3: MRA dosing periods and mean doses per two weeks

	011/317JP N = 11	316/317JP N = 56	011/316/317JP N = 67	324JP N = 82	Total N = 149
Average Dosing period (years)					
n	11	56	67	82	149
Mean	5.035	3.082	3.402	1.199	2.190
SD	1.875	1.287	1.563	0.696	1.601
Min	0.87	0.04	0.04	0.08	0.04
Median	6.100	3.451	3.548	1.191	2.111
Max	6.22	4.21	6.22	2.38	6.22
Total Dosing period (patient years)	55.4	172.6	228.0	98.3	326.3
Average Dose (mg/kg/2week)					
n	11	56	67	82	149
Mean	6.132	7.546	7.314	7.485	7.408
SD	1.527	0.876	1.127	1.358	1.258
Min	3.75	5.35	3.75	4.00	3.75
Median	6.942	7.751	7.645	7.765	7.718
Max	8.19	9.68	9.68	12.19	12.19

Adverse events

In Study WA18221, treatment emergent adverse events (TEAEs) were reported more frequently in the TCZ groups (Table 4). A total of 72 TEAEs were reported in 33 (89.2%) subjects in the 8 mg/kg group, 75 in 33 (86.8%) in the 12 mg/kg and 48 in 23 (62.2%) subjects in the placebo group.

In Study WA18221, infection related AEs were more common in the TCZ groups, with increased reporting in the higher dose group. There were 21 infection related AEs reported in 18 (48.6%) subjects in the 8 mg/kg group, 34 in 23 (60.5%) in the 12 mg/kg group and 14 in eleven (29.7%) in the placebo group (Table 4). Infective AEs were more common in the TCZ groups in general, with a range of different types of infection involved.

The rate of infectious AEs increased with dose. The rate of gastrointestinal AEs was greater in the TCZ groups, particularly diarrhoea and vomiting (Table 4). The rate of AEs did not appear to be influenced by age, gender or disease severity.

Table 4: Summary of adverse events to Week 12 by all body systems, Infections and Infestations, and Gastrointestinal Disorders

Body System/ Adverse Event	Placebo N = 37 No. (%)	TCZ 8 mg/kg N = 37 No. (%)	TCZ 12 mg/kg N = 38 No. (%)	All TCZ N = 75 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	23 (62.2)	33 (89.2)	33 (86.8)	66 (88.0)
Total Number of AEs	48	72	75	147
INFECTIONS AND INFESTATIONS				
Total Pts With at Least one AE	11 (29.7)	14 (37.8)	20 (52.6)	34 (45.3)
UPPER RESPIRATORY TRACT INFECTION	4 (10.8)	4 (10.8)	6 (15.8)	10 (13.3)
NASOPHARYNGITIS	1 (2.7)	2 (5.4)	6 (15.8)	8 (10.7)
GASTROENTERITIS VIRAL	-	1 (2.7)	2 (5.3)	3 (4.0)
PHARYNGITIS	2 (5.4)	1 (2.7)	1 (2.6)	2 (2.7)
VIRAL INFECTION	-	1 (2.7)	1 (2.6)	2 (2.7)
VIRAL UPPER RESPIRATORY TRACT INFECTION	-	1 (2.7)	1 (2.6)	2 (2.7)
INFECTED BITES	1 (2.7)	-	1 (2.6)	1 (1.3)
ARTHRITIS BACTERIAL	-	1 (2.7)	-	1 (1.3)
BRONCHITIS	-	-	1 (2.6)	1 (1.3)
CANDIDIASIS	-	1 (2.7)	-	1 (1.3)
CONJUNCTIVITIS INFECTIVE	-	-	1 (2.6)	1 (1.3)
FOLLICULITIS	-	-	1 (2.6)	1 (1.3)
GASTROENTERITIS	-	-	1 (2.6)	1 (1.3)
HORDEOLUM	-	-	1 (2.6)	1 (1.3)
IMPETIGO	-	-	1 (2.6)	1 (1.3)
ORAL HERPES	-	1 (2.7)	-	1 (1.3)
OTITIS MEDIA VIRAL	-	-	1 (2.6)	1 (1.3)
PNEUMONIA MYCOPLASMAL	-	-	1 (2.6)	1 (1.3)
RHINITIS	-	-	1 (2.6)	1 (1.3)
SINUSITIS	-	1 (2.7)	-	1 (1.3)
TINEA VERSICOLOUR	-	1 (2.7)	-	1 (1.3)
TONSILLITIS	-	1 (2.7)	-	1 (1.3)
TOOTH ABSCESS	-	-	1 (2.6)	1 (1.3)
URINARY TRACT INFECTION	-	1 (2.7)	-	1 (1.3)
VARICELLA	-	-	1 (2.6)	1 (1.3)
ENTEROVIRUS INFECTION	1 (2.7)	-	-	-
FUNGAL SKIN INFECTION	1 (2.7)	-	-	-
FURUNCLE	1 (2.7)	-	-	-
HERPES SIMPLEX	1 (2.7)	-	-	-
INFLUENZA	1 (2.7)	-	-	-
Total Number of AEs	13	17	29	46
GASTROINTESTINAL DISORDERS				
Total Pts With at Least one AE	2 (5.4)	8 (21.6)	6 (15.8)	14 (18.7)
DIARRHOEA	1 (2.7)	3 (8.1)	2 (5.3)	5 (6.7)
VOMITING	-	2 (5.4)	1 (2.6)	3 (4.0)
ABDOMINAL PAIN	-	-	2 (5.3)	2 (2.7)
GASTROINTESTINAL DISORDER	-	2 (5.4)	-	2 (2.7)
ABDOMINAL PAIN UPPER	1 (2.7)	1 (2.7)	-	1 (1.3)
NAUSEA	1 (2.7)	1 (2.7)	-	1 (1.3)
CONSTIPATION	-	1 (2.7)	-	1 (1.3)
DENTAL CARIES	-	-	1 (2.6)	1 (1.3)
EPIGASTRIC DISCOMFORT	-	-	1 (2.6)	1 (1.3)
MOUTH ULCERATION	-	1 (2.7)	-	1 (1.3)
Total Number of AEs	3	11	7	18
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Total Pts With at Least one AE	2 (5.4)	5 (13.5)	7 (18.4)	12 (16.0)
ECZEMA	-	-	3 (7.9)	3 (4.0)
RASH	1 (2.7)	1 (2.7)	1 (2.6)	2 (2.7)
ANGIOEDEMA	-	-	1 (2.6)	1 (1.3)
DERMATITIS	-	1 (2.7)	-	1 (1.3)
DERMATITIS CONTACT	-	-	1 (2.6)	1 (1.3)
DRY SKIN	-	1 (2.7)	-	1 (1.3)
ERYTHEMA	-	-	1 (2.6)	1 (1.3)
RASH PRURITIC	-	1 (2.7)	-	1 (1.3)
SWELLING FACE	1 (2.7)	-	-	-
Total Number of AEs	2	5	8	13

In Study WA18221, MTX use at baseline did not influence the rate of AEs in the TCZ groups: 20 (87.0%) subjects with no MTX use reported AEs compared with 46 (88.5%) with MTX use.

In Study MRA317JP/MRA324JP, a total of 1631 TEAEs were reported in the 149 subjects (all subjects reported at least one AE). The most commonly reported conditions were in the *Infections and Infestations* System Organ Class (SOC), reported in 135 (90.6%) subjects, *Skin and Subcutaneous Disorders*, 100 (67.1%) subjects and *Gastrointestinal Disorders*, 85 (57%) subjects. All types of childhood infections were represented (Table 5). Eczema was reported in 43 (28.9%) subjects.

Table 5: Summary of adverse events by all body systems and Infections and Infestations by intensity and relation to trial treatment - Study MRA317JP/MRA324JP

Body System/ Adverse Event	Adverse Event				Adverse Drug Reactions			
	Mild No. (%)	Moderate No. (%)	Severe No. (%)	Total No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)	Total No. (%)
All Body Systems								
Total Pts with at Least one AE	146(98.0)	58(38.9)	6(4.0)	149(100.0)	143(96.0)	41(27.5)	5(3.4)	145(97.3)
Total Number of AEs	1511	114	6	1631	1182	74	5	1261
INFECTIONS AND INFESTATIONS								
Total Pts with at Least one AE	132(88.6)	29(19.5)	-	135(90.6)	129(86.6)	25(16.8)	-	131(87.9)
ABNORMAL CONJUNCTIVITIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
ARTHRITIS VIRAL	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
BACTERAEMIA	-	1(0.7)	-	1(0.7)	-	1(0.7)	-	1(0.7)
BRONCHIOLITIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
BRONCHITIS	25(16.8)	-	-	25(16.8)	25(16.8)	-	-	25(16.8)
BRONCHITIS ACUTE	11(7.4)	1(0.7)	-	12(8.1)	10(6.7)	1(0.7)	-	11(7.4)
CELLULITIS	2(1.3)	-	-	2(1.3)	2(1.3)	-	-	2(1.3)
CHRONIC SINUSITIS	2(1.3)	1(0.7)	-	3(2.0)	2(1.3)	-	-	2(1.3)
CYSTITIS	3(2.0)	-	-	3(2.0)	3(2.0)	-	-	3(2.0)
DENTAL CARIES	10(6.7)	-	-	10(6.7)	10(6.7)	-	-	10(6.7)
ECZEMA INFECTED	1(0.7)	-	-	1(0.7)	-	-	-	-
ENTEROBIASIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
ERYTHEMA INFECTIOSUM	5(3.4)	-	-	5(3.4)	4(2.7)	-	-	4(2.7)
FOLLICULITIS	5(3.4)	-	-	5(3.4)	3(2.0)	-	-	3(2.0)
FUNGAL SKIN INFECTION	3(2.0)	-	-	3(2.0)	3(2.0)	-	-	3(2.0)
FURUNCLE	-	1(0.7)	-	1(0.7)	-	-	-	-
GASTROENTERITIS	48(32.2)	12(8.1)	-	60(40.3)	48(32.2)	10(6.7)	-	58(38.9)
GASTROENTERITIS ROTAVIRUS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
GASTROENTERITIS VIRAL	10(6.7)	-	-	10(6.7)	10(6.7)	-	-	10(6.7)
HAND-FOOT-AND-MOUTH DISEASE	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
HERPANGINA	3(2.0)	-	-	3(2.0)	3(2.0)	-	-	3(2.0)
HERPES SIMPLEX	4(2.7)	-	-	4(2.7)	3(2.0)	-	-	3(2.0)
HERPES ZOSTER	2(1.3)	4(2.7)	-	6(4.0)	2(1.3)	4(2.7)	-	6(4.0)
HORDEOLUM	15(10.1)	-	-	15(10.1)	15(10.1)	-	-	15(10.1)
IMPETIGO	14(9.4)	-	-	14(9.4)	14(9.4)	-	-	14(9.4)
INFECTION	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
INFECTIOUS MONONUCLEOSIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
INFLUENZA	26(17.4)	-	-	26(17.4)	24(16.1)	-	-	24(16.1)
LARYNGOTRACHEO BRONCHITIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
LICE INFESTATION	1(0.7)	-	-	1(0.7)	-	-	-	-
MOLLUSCUM CONTAGIOSUM	5(3.4)	-	-	5(3.4)	4(2.7)	-	-	4(2.7)
MUMPS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
NASOPHARYNGITIS	87(58.4)	1(0.7)	-	88(59.1)	85(57.0)	1(0.7)	-	86(57.7)
ONPHALITIS	2(1.3)	-	-	2(1.3)	2(1.3)	-	-	2(1.3)
ORAL CANDIDIASIS	6(4.0)	-	-	6(4.0)	6(4.0)	-	-	6(4.0)
OTITIS EXTERNA	4(2.7)	-	-	4(2.7)	4(2.7)	-	-	4(2.7)
OTITIS MEDIA	15(10.1)	-	-	15(10.1)	15(10.1)	-	-	15(10.1)
OTITIS MEDIA ACUTE	4(2.7)	-	-	4(2.7)	4(2.7)	-	-	4(2.7)
PARONYCHIA	20(13.4)	-	-	20(13.4)	18(12.1)	-	-	18(12.1)
PAROTITIS	3(2.0)	-	-	3(2.0)	3(2.0)	-	-	3(2.0)
PERITONSILLAR ABSCESS	-	1(0.7)	-	1(0.7)	-	1(0.7)	-	1(0.7)
PHARYNGITIS	48(32.2)	2(1.3)	-	50(33.6)	45(30.2)	2(1.3)	-	47(31.5)
PNEUMONIA	7(4.7)	3(2.0)	-	10(6.7)	7(4.7)	3(2.0)	-	10(6.7)
RASH PUSTULAR	1(0.7)	1(0.7)	-	2(1.3)	1(0.7)	1(0.7)	-	2(1.3)
RHINITIS	14(9.4)	-	-	14(9.4)	14(9.4)	-	-	14(9.4)
SINUSITIS	5(3.4)	-	-	5(3.4)	5(3.4)	-	-	5(3.4)
SKIN INFECTION	3(2.0)	-	-	3(2.0)	3(2.0)	-	-	3(2.0)
SUBCUTANEOUS ABSCESS	7(4.7)	1(0.7)	-	8(5.4)	7(4.7)	1(0.7)	-	8(5.4)
TINEA NIGRA	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
TINEA PEDIS	2(1.3)	-	-	2(1.3)	2(1.3)	-	-	2(1.3)
TONSILLITIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
UPPER RESPIRATORY TRACT INFECTION	69(46.3)	-	-	69(46.3)	68(45.6)	-	-	68(45.6)
URINARY TRACT INFECTION	3(2.0)	1(0.7)	-	4(2.7)	3(2.0)	1(0.7)	-	4(2.7)
VARICELLA	3(2.0)	-	-	3(2.0)	3(2.0)	-	-	3(2.0)
VIRAL INFECTION	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
VULVITIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
WOUND INFECTION	-	1(0.7)	-	1(0.7)	-	1(0.7)	-	1(0.7)
ABSCESS LIMB	7(4.7)	-	-	7(4.7)	6(4.0)	-	-	6(4.0)
BETA HAEMOLYTIC STREPTOCOCCAL INFECTION	3(2.0)	1(0.7)	-	4(2.7)	3(2.0)	1(0.7)	-	4(2.7)
GINGIVAL ABSCESS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
CAMPYLOBACTER INTESTINAL INFECTION	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
SKIN CANDIDA	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
DACRYOCYSTITIS INFECTIVE	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
ENTERITIS INFECTIOUS	4(2.7)	-	-	4(2.7)	4(2.7)	-	-	4(2.7)
CYTOMEGALOVIRUS VIRAEMIA	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
TINEA INFECTION	4(2.7)	-	-	4(2.7)	4(2.7)	-	-	4(2.7)
MYCOPLASMA INFECTION	2(1.3)	-	-	2(1.3)	2(1.3)	-	-	2(1.3)
ENTEROCOLITIS VIRAL	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
Total Number of AEs	530	32	-	570	519	28	-	547
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
SQUAMOUS CELL CARCINOMA	1(0.7)	-	-	1(0.7)	-	-	-	-
SKIN PAPILLOMA	2(1.3)	-	-	2(1.3)	2(1.3)	-	-	2(1.3)
Total Number of AEs	3	-	-	3	2	-	-	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
Total Pts with at Least one AE	11(7.4)	3(2.0)	1(0.7)	13(8.7)	8(5.4)	3(2.0)	1(0.7)	12(8.1)
ANAEMIA NOS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
LYMPHADENITIS	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
LYMPHADENOPATHY	1(0.7)	-	-	1(0.7)	1(0.7)	-	-	1(0.7)
HISTIOCYTOSIS HAEMATOPHAGIC	-	1(0.7)	-	1(0.7)	-	1(0.7)	-	1(0.7)
Total Number of AEs	11	3	1	15	9	3	1	13

In Study MRA317JP/MRA324JP, there were 45 events categorized as infusion reactions reported in 24 (16.1%) subjects: chills in seven (4.7%) subjects, pyrexia in six (4.0%), vomiting and headache in five (3.4%), nausea, pruritus and infusion related reaction in three (2.0%), rhinitis, anaphylactoid reaction, flushing and exanthem in two (1.3%), and dizziness, drug eruption, chest pain, malaise and blood pressure decreased in one (0.7%).

Serious adverse events and deaths

In Study WA18221, serious adverse events (SAEs) were reported in one (2.7%) subject in the 8 mg/kg group (bacterial arthritis), two (5.3%) in the 12 mg/kg (varicella and angioedema/urticaria), and none (0%) in the placebo. There were no deaths.

In Study MRA317JP/MRA324JP, there were 105 SAEs reported in 62 (41.6%) subjects. The most commonly reported group of SAEs were in the *Infections and Infestations* SOC: 29 (19.5%) subjects. The most commonly reported infections were gastroenteritis, reported in 12 (8.1%) subjects and pneumonia, reported in five (3.4%) subjects.

In Study MRA317JP/MRA324JP, two subjects died: one as a result of histiocytosis haematophagic (macrophage activation syndrome) and one due to amyloidosis.

Laboratory findings

In Study WA18221, the rate of abnormal laboratory test results reported as AEs was greater in the TCZ groups: for example, elevated transaminases and decreased neutrophil count (two subjects in the 12 mg/kg group). Alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN) was reported for three (8.1%) subjects in the 8 mg/kg group, one (2.6%) in the 12 mg/kg group and none in the placebo. Aspartate aminotransferase (AST) ≥3 times ULN was reported only for two (5.4%) subjects in the 8 mg/kg group. Sustained elevation in serum cholesterol occurred in one subject in each of the TCZ treatment groups (2.7% for 8 mg/kg and 2.6% for 12 mg/kg).

In Study MRA317JP/MRA324JP, elevated ALT was reported as an AE in 33 (22.1%) subjects and elevated AST in 26 (17.4%). Decreased lymphocyte count was reported in 25 (16.8%) subjects and decreased neutrophil count in 18 (12.1%). Mean laboratory parameters were stable during the studies.

Immunological events

In Study WA18221, one subject in the 12 mg/kg group developed neutralising antibodies by Week 12. Urticaria and angioedema were more common in the TCZ groups.

In Study MRA317JP/MRA324JP, *Immune System Disorders* were reported in 13 (8.7%) subjects. Anaphylactic reaction was reported in two (1.3%) subjects and drug hypersensitivity in one (0.7%).

Discontinuation due to adverse events

In Study WA18221, one subject, originally in the placebo group but subsequently on TCZ 12 mg/kg as escape therapy, withdrew because of haemophagocytic histiocytosis. One subject in the 12 mg/kg group withdrew because of angioedema.

In Study MRA317JP/MRA324JP, ten subjects withdrew because of AEs: anaphylactoid reaction (2), infusion reaction (2), histiocytosis haematophagic (1), amyloidosis (1), duodenal perforation (1), gastrointestinal haemorrhage (1), herpes zoster (1) and increased ALT (1).

Evaluator's overall conclusions on clinical safety

Overall, AEs are more frequent in subjects treated with TCZ, particularly infective AEs. The risk of all types of infection is increased. The risk increases with dose. The SAEs reported in Study WA18221 were either infective or immunologically mediated. In Study MRA317JP/MRA324JP the most commonly reported group of SAEs was infective.

Macrophage activation syndrome, resulting in death, was reported in one subject in Study MRA317JP/MRA324JP.

Elevation in ALT and AST is more common in subjects treated with TCZ but this does not appear to translate to an increased incidence of liver disease. Increased serum cholesterol was also reported in a small number of study subjects.

Urticaria, angioedema and anaphylaxis have been reported in the paediatric population treated with TCZ.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

1. The description of the population pharmacokinetic analysis contained in the report for Study WA18221 did not provide clearance, volume of distribution or $t_{1/2}$ but these parameters were reported in the Product Information (PI) document. The sponsor must provide a report of the population pharmacokinetic analysis from Study WA18221 that includes all of the final parameter estimates (including clearance, volume of distribution and $t_{1/2}$) and also methodology; model development; model selection criteria; and inter-individual and residual error estimates for the population pharmacokinetic analysis from Study WA18221.

2. The efficacy and adverse events sections of the PI refer to the open label extensions for Study WA18221 but these data were not presented in the submission. Instead the long term efficacy data presented in the submission were from Study MRA317JP/MRA324JP. The sponsor will need to clarify which studies actually provided the long term efficacy and safety data referred to in the PI and if the data were from Study WA18221 the sponsor will need to provide summary data for efficacy and tabulations for TEAEs, SAEs, deaths, DAEs and clinically significant abnormalities in laboratory tests from the open label extensions (the 92 week single arm open label extension and/or the 3 year open label continuation phases) of that study.

3. The statistical analysis for CHAQ-DI was referred to in the PI but was not presented in the submission. A table of the results of the statistical analysis for CHAQ-DI must be provided.

4. It was not clear from the submitted data whether co-medication with MTX contributed to either improved efficacy or increased risk of TEAEs. It is important for prescribers to have access to this information in order to decide whether to continue MTX in subjects commencing tocilizumab. How many subjects in Study MRA317JP/MRA324JP were treated with MTX and can the sponsor provide an analysis of efficacy stratified by MTX co-medication? Can the sponsor provide tabulations of TEAEs from Study WA18221 for subjects co-medicated with MTX compared to those that were not?

Supplementary Data

In response to the List of Questions, supplementary data were provided by the sponsor.

Population pharmacokinetic analysis of data from Study WA18221

The serum samples were collected during the 12 week randomised treatment phase of Study WA18221 (Study WA18221 Part 1). The subjects were 75 children aged 2 to 17 years. Pre-dose (trough) samples were collected on study days 8, 15, 29, 43, 57, 71, 78, and 85. Post dose (peak) samples were collected on study days 1, 15, 29 and 71. TCZ was quantified using a LC-MS method.

The pharmacometric analysis was performed using SAS for data management, NONMEM version VI for nonlinear mixed effects modelling and SPLUS for the analysis of output data.

The structural pharmacokinetic model was a two compartment model with concurrent saturable and non-saturable elimination pathways. The Michaelis constant (Km) for the saturable elimination pathway was fixed at 2.47 mg/L, and was not estimated by the model. This model was based on prior data and analyses from an adult population which were not provided in the report. The error model used interindividual variability terms for clearance and volume of distribution, and combined additive and multiplicative

residual variability terms. The covariate model used body surface area as a scaling variable. A first order estimation method was used.

The estimates of the pharmacokinetic parameters and error terms are presented in Table 6. The 95% CIs indicate the parameters were estimated with sufficient precision. The estimates of the parameters are consistent with those presented in the PI. However, the actual estimates for clearance and half-life that are presented in the PI were not presented in the report.

Table 6: Summary of population PK parameters

PK parameter	VALUE	SE	CI 5%	CI 95%
CL (L/d)	0.17	0.0079	0.15	0.19
Q (L/d)	4.6	0.43	3.8	5.4
V_c (L)	0.94	0.051	0.84	1
V_p (L)	1.6	0.085	1.4	1.8
Km (mg/L)	2.5	0	0	2.5
V_{max} (mg/d)	3.4	0.49	2.4	4.4
CL_BSA	0.99	0.087	0.82	1.2
Vc_HGT	2	0.23	1.5	2.5
Vc_Age	0.22	0.11	0.0044	0.44
Additive error (mg/L))	3.6	0.46	2.7	4.5
Multiplicative error (%)	0.15	0.012	0.13	0.17

Evaluator's overall conclusions on supplementary pharmacokinetic data

The data collected, consisting of two point data (peak and trough), would have been suitable for estimating the parameters for a one compartment first order elimination model but were unsuitable for the estimation of a two compartment, combined first order and Michaelis Menten elimination model. A considerable proportion of the data should have been mid-dose, in addition to peak and trough, to enable estimation of such a model. In addition, clearance is written in the model as a "constant" parameter, whereas if there is any component of Michaelis Menten elimination then clearance cannot be a constant (nor can half-life). However, the analysis might still be able to provide an estimate of the effects of body size and age upon volume of distribution and total clearance. Half-life might then be calculated as a secondary parameter from volume of distribution and clearance.

In the final model, clearance was (0.17 x BSA)/0.87 L/day. This corresponds with approximately 8 mL/h (assuming BSA as 1 m^2). This is consistent with the information in the PI. Mean half-life would then be around 19 days, which is consistent with the information in the PI. The estimates of volume of distribution from the model are presented in the PI. The population pharmacokinetic analysis was adequate.

CHAQ-DI score

In Study WA18221 the outcome measures with regard to CHAQ-DI were:

- The percentage CFB in CHAQ-DI score at Week 12
- The proportion of subjects with a minimally important improvement in the CHAQ-DI by Week 12

In the efficacy section of the PI the sponsor refers to the proportion of subjects with a minimally important improvement in the CHAQ-DI. In the supplementary table provided by the sponsor there were seven (18.9%) subjects in the placebo group and 58 (77.3%) in the TCZ with a minimally important improvement in CHAQ-DI score; weighted difference

(95% CI) 56.3 (39.6 to 73.0) p <0.0001. This is consistent with the information provided in the PI.

Long term efficacy data from study WA18221

In the PI the sponsor refers to long term efficacy data from Study WA18221 that was not provided in the submission. In response, the sponsor stated that this information was provided in its *Summary of Clinical Efficacy*. In the *Summary of Clinical Efficacy,* the sponsor described long term efficacy data for Study WA18221 using a cut-off point corresponding to 50 subjects having completed one year of exposure to TCZ. This was not a predefined time point in the study protocol.

A total of 112 subjects were treated with TCZ in Part II of the study. Fifty subjects were exposed for one year or more. Of these subjects 78 (69.6%) had previous or ongoing MTX use. For the primary efficacy outcome measure, JIA ACR30 response with absence of fever, 50 (89.3%) of subjects treated at Week 60 had achieved this outcome. Response was maintained for up to 72 weeks (Figure 8). JIA ACR 90 response rate increased for up to 72 weeks of treatment (Figure 9). No subjects were identified as having loss of response due to the development of neutralizing anti-tocilizumab antibodies.

Figure 8: Proportion of patients achieving JIA ACR30 response with absence of fever at visits up to Week 72 in WA18221 (ITT Population)

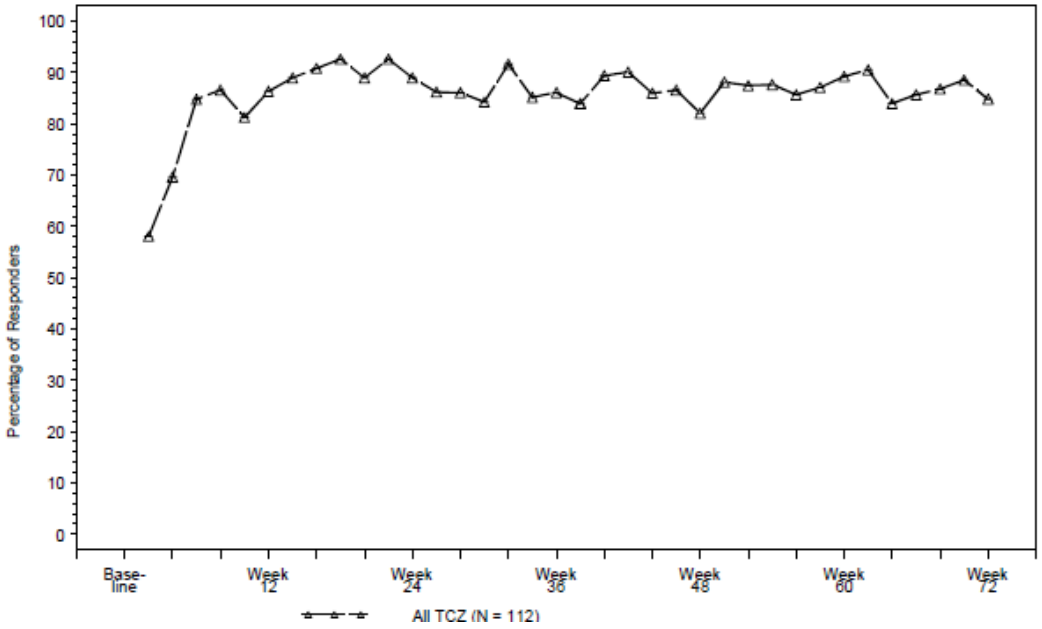
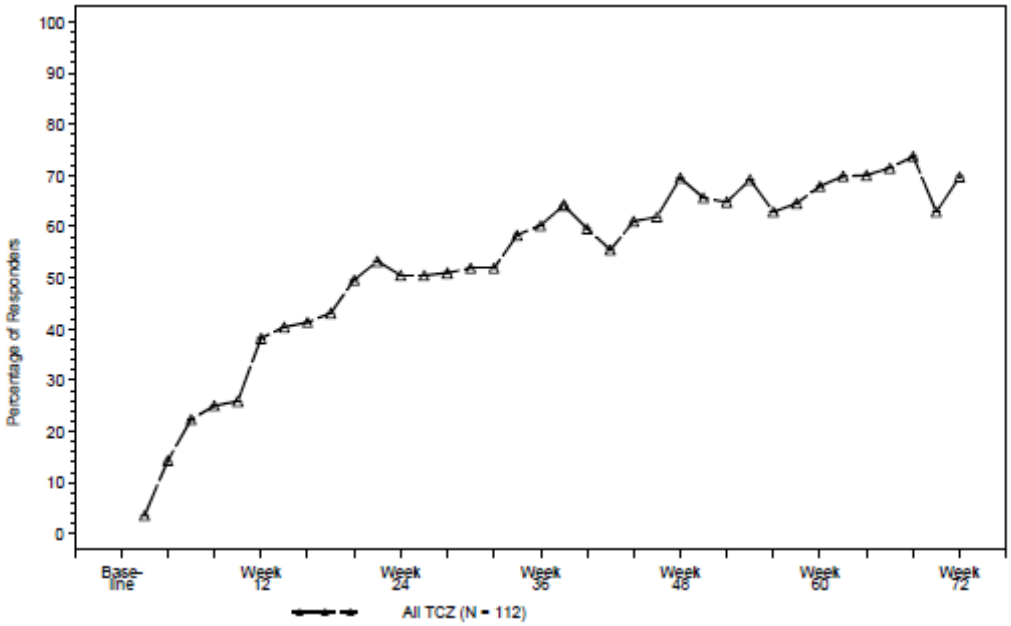


Figure 9: Proportion of patients achieving a JIA ACR90 response at visits up to Week 72 in WA18221 (ITT population)



Effect of MTX on efficacy in Study MRA317JP/MRA324JP

The sponsor stated that MTX treatment was an exclusion criterion for Study MRA317JP/MRA324JP and that the effect of concomitant medication with MTX and TCZ cannot be determined from this study.

Long term safety data for study WA18221

The long term safety data for Study WA18221 was stated by the sponsor to be discussed in its *Summary of Clinical Safety*. There were 112 children exposed to TCZ, with 50 exposed for greater than one year. The total duration of observation was 132.4 patient years. The median (range) age of the subjects was 10 (2 to 17) years.

TEAEs

TEAEs were reported in 110 (98.2%) subjects. The most commonly reported TEAEs were nasopharyngitis and upper respiratory tract infection (URTI).

SAEs

A total of 32 SAEs were reported in 25 (22.3%) subjects. There were three (2.7%) subjects with haemophagocytic histiocytosis, three (2.7%) with varicella and three (2.7%) with gastroenteritis.

Deaths

There was one death reported: tension pneumothorax in a 16 year old male.

Laboratory findings

Neutropenia was reported in 20 (17.9%) subjects and one subject had an abnormally low platelet count. Thirteen (11.6%) subjects had elevations of ALT.

Immunological AEs

There were eleven AEs reported during infusion of tocilizumab in nine subjects: infusion related reaction (3), angioedema (1), rash (1), asthenia (1), catheter site erythema (1), puncture site pain (1), vomiting (1), musculoskeletal pain (1) and somnolence (1).

Withdrawal due to AEs

Two subjects withdrew from the extension of Study WA18221 due to AEs: one due to increased ALT; one due to pulmonary veno-occlusive disease.

Adverse event rate and concomitant MTX

In the 12 week double blind phase, in subjects treated with MTX at baseline TEAEs were reported in 15 (57.7%) subjects treated with placebo and 46 (88.5%) treated with TCZ; and in those not treated with MTX at baseline eight (72.7%) subjects treated with placebo and 20 (87%) subjects treated with TCZ. In subjects treated with TCZ, infections were reported in 27 (51.9%) treated with MTX and seven (30.4%) subjects not treated with MTX at baseline. In the long term extension data, the rate of TEAEs was 820.9/100 patient years in subjects treated with MTX at baseline and 958.4/100 patient years in those not treated with MTX at baseline.

Additional postmarketing data

There has been a case report to the TGA of a death during the 92 Week extension phase of Study WA18221.

The death occurred in a 6 year old male treated with TCZ 12 mg/kg. The death occurred 714 days after commencing TCZ and 10 days after the last dose. The patient became unconscious and died; the cause was unknown. There was concomitant treatment with MTX and also ibuprofen. There may have been concurrent gastroenteritis as the patient had vomited twice, but vomiting is non-specific in children. The event term was amended by the investigator from “death” to “fatal septicaemia”.

Clinical Summary and Conclusions

Clinical aspects

The increases in serum concentrations of IL-6 and sIL-6R are consistent with the proposed mechanism of action of TCZ. Response to TCZ did not appear to be related to the magnitude of TCZ exposure. Hence there would be no benefit in monitoring serum TCZ concentrations.

Benefit risk assessment

Benefits

Study WA18221 demonstrated efficacy for TCZ in children and adolescents with sJIA over a 12 week period. The treatment effect was clinically significant to the extent that the study subjects had marked improvement in all of the study measures. There was no apparent difference in efficacy between subjects treated with MTX and those who were not. CS dose and MTX did not appear to influence efficacy. Efficacy appeared to be maintained for up to 72 weeks. Efficacy was demonstrated for each of the age groupings 2 to 5 years, 8 to 12 years and 13 to 18 years.

Study MRA317JP/MRA324JP indicated that efficacy persisted for up to 324 weeks. However, because the study was not placebo controlled it is not clear to what extent the response rate might have been influenced by the natural history of sJIA, that is, the proportion of subjects that might have undergone spontaneous remission.

Risks

Overall, AEs are more frequent in subjects treated with TCZ, particularly infective AEs. The risk of all types of infection is increased. This includes serious infection and infection leading to death. The risk increases with dose. The SAEs reported in Study WA18221 were either infective or immunologically mediated. In Study MRA317JP/MRA324JP the

most commonly reported group of SAEs was infective. It is not clear to what extent the risks of AEs and infections are increased by concomitant treatment with MTX.

Macrophage activation syndrome, resulting in death, was reported in one subject in Study MRA317JP/MRA324JP. Haemophagocytic histiocytosis was reported in three subjects during the extension to Study WA18221.

Elevation in ALT and AST is more common in subjects treated with TCZ but this does not appear to translate to an increased incidence of liver disease. Increased serum cholesterol was also reported in a small number of study subjects.

Urticaria, angioedema and anaphylaxis have been reported in the paediatric population treated with TCZ.

Balance

TCZ offers a marked improvement in efficacy for subjects with sJIA, at the expense of an increase in the risk of all infections, including serious infections. Overall, the risk benefit balance is in favour of TCZ. The benefit appears to persist for up to 72 weeks. Hence, in a condition with considerable morbidity TCZ offers a marked improvement in long term outcome.

Conclusions

Tocilizumab (Actemra) should be approved for the indication:

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

Conditions for registration

Extension of indications to sJIA in the paediatric population should be conditional on the sponsor providing timely updates of the efficacy and safety data arising from the ongoing studies: Study WA18221 and Study WA19977.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The summary of the Ongoing Safety Concerns in adults as specified by the sponsor is shown in Table 7.

Table 7: Ongoing safety concerns in adults

Category	Safety Concern	Comment
Important Identified Risks	Serious infection	Observed with tocilizumab and other biological DMARDs.
	Complications of diverticulitis (including GI perforation)	Risk increased with RA, use of corticosteroids and/or NSAIDs. Observed with tocilizumab and other biological DMARDs.
	Serious hypersensitivity reactions	Observed with tocilizumab and other biological DMARDs.
Important Potential Risks	Neutropenia	Observed with tocilizumab and other biological DMARDs.
	Thrombocytopenia	Observed with tocilizumab and other biological DMARDs.
	Elevated hepatic transaminases	Observed with tocilizumab and other biological DMARDs. Elevated bilirubin (essentially indirect) observed with tocilizumab; linked to Gilbert's variants; no clinical consequences.
	Elevated lipids	Observed with tocilizumab.
	Elevated bilirubin (essential indirect)	Observed with tocilizumab; linked to Gilbert's variants; no clinical consequences.
	Immunogenicity	Observed with tocilizumab; clinical relevance needs further evaluation
	Malignancies	Based on increased risk in RA and with other biological DMARDs; no imbalance noted for TCZ.
	Demyelinating disorders	Based on increased risk with other biological DMARDs; 2 cases seen with TCZ.
	CYP450 enzyme normalisation	Hypothetical risk – of greater relevance to agents with a narrow therapeutic index which are subject to regular monitoring of effect or concentration, and dosage adjustment, as standard clinical practice. Risk applies at initiation and withdrawal of tocilizumab treatment.
	Elderly	No clinical evidence of increased risk; no difference in PK
	Paediatric patients	Paediatric program ongoing (PIP approved).
	Effects during pregnancy	Use in pregnancy not recommended.
	Hepatic impairment	Caution to be exercised in this subgroup; tocilizumab not subject to hepatic metabolism.
	Renal impairment	No dose adjustment required; tocilizumab not subject to renal elimination. No effect of mild renal impairment noted with tocilizumab. No formal study in patients with mild to moderate renal impairment.
	Combination with biologics	Study ongoing: rituximab + tocilizumab.

Category	Safety Concern	Comment
Important Potential Risks (cont'd)		
	Vaccinations	Efficacy of proteinaceous and polysaccharide vaccines to be studied in concomitant use with tocilizumab.
	Increased mortality in the Japanese PMS compared to clinical study poulation	Observation likely to reflect population being exposed. Patients are elderly with significant concurrent medical disease and multiple concomitant medications.

The sponsor also presented a summary of the Ongoing Safety Concerns in paediatric patients (Table 8).

Table 8: Ongoing Safety Concerns in paediatric patients

Category	Safety Concern	Comment
Important Identified Risks	Serious infection	Observed with tocilizumab and other biological DMARDs.
	Serious hypersensitivity reactions	Observed with tocilizumab and other biological DMARDs.
Important Potential Risks	Skeletal development	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.
	Immunogenicity	Observed with tocilizumab; clinical relevance needs further evaluation.
	Malignancies	Based on increased risk in RA and with other biological DMARDs; no imbalance noted for TCZ.
	CYP450 enzyme normalisation	Hypothetical risk – of greater relevance to agents with a narrow therapeutic index which are subject to regular monitoring of effect or concentration, and dosage adjustment, as standard clinical practice. Risk applies at initiation and withdrawal of tocilizumab treatment.

Nonclinical comments

The nonclinical evaluator noted that the results and conclusions drawn from the nonclinical program for tocilizumab detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the evaluator.

Clinical comments

The clinical evaluator noted that the potential risks in children should also included failure of vaccine effect.

OPR reviewer comment:

The summary of ongoing safety concerns provided by the sponsor includes serious infections and serious hypersensitivity reactions as important identified risks in adults and children. Other safety concerns raised by the clinical evaluator in the clinical evaluation report were also included in the ongoing safety concerns.

It was not immediately apparent to the OPR evaluator why there were differences in the ongoing safety concerns between adult and paediatric populations, specifically, why the safety concerns listed as identified or potential risks in adults were not considered to be identified or potential risks in paediatric populations. The sponsor provided the following justification:

"The intent of the *Summary of Ongoing Safety Concerns in Paediatric Patients* was to characterise particular concerns for the sJIA indication and paediatric patients that were raised by the EU Committee on Medicinal Products for Human Use (CHMP). As the Safety Specification indicates, many of the safety concerns in adults were also observed in paediatric subjects in study WA18221 therefore the *Summary of Ongoing Safety Concerns in Adult Patients* also pertains to the paediatric population. The safety profile in sJIA patients is considered similar to that of adult RA patients and the same events of special interest are therefore applicable."

The OPR evaluator was satisfied with the sponsor's justification and concluded that for the purposes of this evaluation, the ongoing safety concerns in adults are also considered to be ongoing safety concerns in paediatric populations.

The sponsor committed to rectify the omission of the title 'important missing information' from the summary of ongoing safety concerns. The following safety concerns will be listed as important missing information, rather than important potential risks: elderly, paediatric patients, effects during pregnancy, hepatic impairment, renal impairment, combination with biologics, vaccinations and increased mortality in the Japanese PMS. Any other relevant information since the last data lock point will also be provided in the updated version of the RMP.

Overall, the summary of ongoing safety concerns was accepted.

Pharmacovigilance plan

The sponsor proposed to undertake both routine and additional pharmacovigilance for a number of the identified ongoing safety concerns.[11]

As additional pharmacovigilance activities the sponsor has stated that they will undertake the following:

- Ongoing and planned clinical trial program
- Pharmacoepidemiology board
- Guided Questionnaires
- Patient Registries/Observational Studies
    - British Society of Rheumatology Biologics Register (BSRBR)
    - Swedish registry (Anti-Rheumatic Therapy in Sweden [ARTIS])
    - German registry (RABBIT)
    - European Network of Teratology Information Services (ENTIS)
    - Paediatric Rheumatology in Europe Society
    - Planned Arthritis Research Council Paediatric Biologicals Registry
    - Pregnancy registry OTIS (US)

[11] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- US Claims database

The OPR reviewer had no objection to the sponsor undertaking the pharmacovigilance activities outlined above. Information provided by the sponsor indicates that the guided questionnaires will be used for designated serious and non-serious AEs in all spontaneous cases and in all clinical trials, including post-marketing studies.

The sponsor provided information on the process for development of the guided questionnaires and outlined the measures for maintaining and updating them and also for measuring the effectiveness of their use as an additional pharmacovigilance activity.

With regards to the proposed patient registries and observational studies, the sponsor stated that sJIA is a rare disease and that the sponsor plans to use data as it becomes available from the Paediatric Rheumatology in Europe Society. Furthermore, given the rarity of sJIA and the diversity of multiple populations in EU, this is presently the only feasible option to study long term safety of biologic therapies in sJIA. Data on sJIA prevalence, clinical features and therapy in Australia suggest no important differences in characteristics of sJIA between Australia and Europe. Hence, findings from the aforementioned multicentre registry will be applicable to the Australian population and will adequately characterise long term safety of Actemra in sJIA. The sponsor does not intend to establish or utilise any Australian registries as the data that will be obtained from the European registries can adequately characterise the long term safety of Actemra.

The sponsor further supported these conclusions by providing the following information from the Australian Institute of Health and Welfare (AIHW):[12]

The overall prevalence of juvenile arthritis in Australia was estimated at 103 cases per 100,000, which corresponds to a total of approximately 22,000 cases of juvenile arthritis in Australia. sJIA accounts for 6% to 11% of all JIA, yielding an estimated prevalence of 1300 to 2400 patients with sJIA in Australia. In reality this number is probably much lower since it is based on survey results not on clinically confirmed sJIA and at a given point in time. Only a fraction of these patients (5%-10%) will be starting Actemra each year and available for enrolment in a registry. In order to monitor postmarketing safety a registry should be able to enrol a sufficient number of patients for analysis. In the absence of an established JIA registry setting up a new registry is not feasible due to the low number of sJIA patients eligible to be enrolled in such a registry.

The sponsor concluded that there is no reason to believe that clinical characteristics, diagnostic activities and treatment practice are significantly different in Australia than in the countries where there are established or actively planned biological DMARD and/or sJIA registries. The sponsor's detailed justification for the use of international registries and the assurance that the data from these registries is applicable to the Australian population was accepted.

Risk minimisation activities

In evaluating the need for risk minimisation activities, the sponsor provided details of the routine risk minimisation activities that will be undertaken for most of the identified safety concerns and provided a justification for why they consider routine activities are sufficient.[13]

[12] Australian Institute of Health and Welfare 2008. Juvenile arthritis in Australia. Arthritis series no. 7. Cat. no. PHE 101. Canberra: AIHW.

[13] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The sponsor concluded that routine risk minimisation activities are not sufficient for the important identified risk: serious hypersensitivity reactions. The sponsor proposed to provide information and educational resource materials to those preparing, administering and monitoring infusions as an additional risk minimisation activity for this important identified risk.

The OPR reviewer accepted the sponsor's justifications and evaluation of the need for risk minimisation activities.

For the important identified risk serious hypersensitivity reactions the sponsor has proposed to undertake additional risk minimisation activities. The sponsor has prepared an information program to support the treatment of rheumatoid arthritis.

The information program is designed to mitigate risk by minimising the potential for medication errors and/or clinically important infusion reactions by training the personnel involved in the preparation and administration of infusions, providing background information on the risks, and addressing safe use of the product. The program is directed towards the training of infusion nurses at the different sites where the drug may be administered. The education materials will also be provided to prescribers and, where appropriate, to patients.

The sponsor stated that the objective of the information program is to ensure that those administering infusions are trained in the appropriate procedure for administering infusions, are familiar with the potential hypersensitivity reactions, and are able to recognise the symptoms and initiate appropriate measures promptly. To further educate personnel responsible for administering infusions that immediately before administration, they should ensure that there are no circumstances mitigating against administration of Actemra, such as presence of an active infection or a previous hypersensitivity reaction.

The information program encompasses information materials for infusion nurses, reference information and tools provided at the physician's office and/or the infusion centre. The sponsor also provided information on the method of delivery of the information program.

The sponsor will assess the effectiveness of the proposed measures by monitoring the number of adverse events associated with medication errors and infusion reactions. The number of such events will be documented in the Periodic Safety Update Report (PSUR) and the frequency, nature and pattern monitored by the sponsor. The rate and nature of the events will be monitored to identify any increases in the reporting rate, changes in the nature of the events reported and information about the timeliness and adequacy of the treatment provided to patients. The sponsor indicated that it is most appropriate to continue risk minimisation activities and to closely monitor adverse events of interest and that ongoing monitoring of the rate and severity of events will be balanced with the overall benefit profile of Actemra.

The OPR reviewer had no objection to the sponsor implementing the educational program as outlined for the RA indication. However, with regards to the education program for the sJIA indication, the sponsor stated that they are "currently evaluating whether to utilise infusion centres for patients with sJIA. The infusion centres have been set up to facilitate access to the medication for RA patients who would otherwise be unable to obtain treatment in the hospital setting. It is expected that the number of patients to be treated for sJIA will be low and consequently there will be limited requirement to use the infusion centres."

Upon making a decision as to whether to use the infusion centres for patients with sJIA, the sponsor should be required to inform the TGA of their decision. If the sponsor intends

to use the infusion centres for patients with sJIA, they should be required to provide OMA and OPR with a justification for this decision which specifically addresses the additional concerns associated with administering Actemra in a vulnerable paediatric population.

Conditions of Registration

On 13 January 2011 approval for the extension of indication was granted.[2] Attached to the approval letter were a number of specific conditions of registration. Specifically, conditions 10-14 state:

10. Referral by the Delegate, via the Office of Product Review, to the Advisory Committee on the Safety of Medicines (ACSOM) for the latter's recommendations regarding the extent to which resuscitation facilities should be required during the administration of Actemra to a patient.

11. The development and implementation of an Australian specific Risk Management Plan (RMP), in particular an RMP which addresses, to the satisfaction of the delegate and of the Office of Product Review (OPR), the risk of anaphylaxis with Actemra and the appropriate management of that risk.

12. The sponsor is required to write to all three of the following organizations, the Australian and New Zealand College of Anaesthetists, the Australian Resuscitation Council and the Australian Immunology Society, seeking their advice on the development of a suitable safety protocol for the administration of Actemra, a protocol which addresses in particular the risk of anaphylaxis to Actemra.

13. The sponsor is required to provide regular updates on the progress of the consultation process with the three organizations named at the previous dot point, these updates to be provided every 2 months to both the Prescription Medicines Clinical Unit 3 (PMCU 3) of the Office of Medicines Authorisation (OMA) and to the Office of Product Review (OPR) of the TGA.

14. A safety protocol, developed by the consultation process referred to under points 12 and 13, will be required to be submitted for review by both the Prescription Medicines Clinical Unit 3 (PMCU 3) and the Office of Product Review (OPR) no later than six months after the date of the approval letter for this application.

Conditions 12-14 relate to the risk minimisation plan. These conditions required the sponsor to write to multiple organisations and seek their advice on the development of a suitable safety protocol for the administration of Actemra, a protocol which addresses in particular the risk of anaphylaxis to Actemra.

The sponsor has provided regular updates to the TGA on the outcomes of their discussions with the Australian Resuscitation Council (ARC), the Australasian Society for Immunology (ASI), the Australian and New Zealand College of Anaesthetists (ANZCA) and the Australian Society of Clinical Immunology and Allergy (ASCIA).

A member of the ASCIA agreed to work with the sponsor. The ASCIA member was provided with a copy of the current Actemra Infusion Program standard operating procedure (SOP) and asked to comment of the appropriateness of the SOP and the anaphylaxis flow chart. The ASCIA member provided feedback and the sponsor states that they have adopted the suggested changes.

The sponsor subsequently provided a copy of the proposed safety protocol and associated training documents to the TGA for review (as per condition 14). The sponsor also stated

that they have received feedback from the ANZCA stating that their request for advice is scheduled for review at a meeting of the ANZCA secretariat. It was recommended that the sponsor be required to update the TGA upon receipt of this feedback and detail any further actions/revisions to the protocol that arise as a result.

The OPR reviewer noted that the sponsor has had some success in liaising with expert organisations and was reassured that the safety protocol has been developed with expert consultation and input. The OPR reviewer had not evaluated the clinical components of the safety protocol, rather it has been reviewed to ensure consistency with all of the information the sponsor has provided regarding Actemra infusions in the RA indication.

As per the advice of the Advisory Committee on the Safety of Medicines (ACSOM) and in order to ensure consistency, it was recommended that the sponsor be required to update the protocols. In addition, to ensure uniformity of the sponsor's proposed protocol with current clinical guidelines, it was recommended that the sponsor be required to provide evidence that the anaphylaxis protocol included as part of the safety protocol is consistent with the Therapeutic Guidelines: Emergency Medicine and/or the ARC guidelines for the management of anaphylaxis.

Advice from the Advisory Committee on the Safety of Medicines

As per Condition 10, advice was obtained from the ACSOM regarding the extent to which resuscitation facilities should be required during administration of Actemra to a patient.

ACSOM agreed that infusion in a hospital setting would provide the greatest certainty that appropriate equipment and appropriately skilled staff would be present to recognise and respond to serious hypersensitivity events. However, recognised that this might not be practical, and suggested the following measures could be considered to support prompt and appropriate patient management in the event of a serious hypersensitivity reaction or anaphylaxis:

- Infusions given by qualified registered nurses;
- Equipment and pharmacotherapy is available at infusion centres to initiate resuscitation until paramedic transfer;
- Infusion centre staff have immediate access to a qualified medical officer available to administer resuscitation activities (similar to systems in place at outpatient radiology centres where adverse reactions to contrast media may occur or at allergen/food challenge clinics); and,
- Training is provided to infusion centre staff in recognising hypersensitivity and responding to patient deterioration (such as the program 'Recognising and Responding to Clinical Deterioration' provided by the Australian Commission on Safety and Quality in Health Care).

The information provided by the sponsor demonstrated that infusions are given by qualified registered nurses, that equipment and pharmacotherapy is available at infusion centres to initiate resuscitation until paramedic transfer and that training is provided to infusion centre staff in recognising hypersensitivity and responding to patient deterioration.

The sponsor provided the following response regarding ACSOM's advice that infusion centre staff regarding immediate access to a qualified medical officer:

"No, infusion centre nurses do not have immediate access to a qualified medical officer. In the event of a hypersensitivity reaction, including anaphylaxis, the following practices are in place to manage any such reaction and to allow the initiation of appropriate treatment

until the paramedics arrive. The sponsor's third party partner utilises registered nurses who are experienced in the administration of infusional drugs, are qualified in cannulation techniques and have current certification in CPR and the First Aid Management of Anaphylaxis. These nurses receive specific training on the rheumatoid arthritis disease state, the Actemra PI and the Actemra Infusion and First Aid Management of Anaphylaxis Protocols, which include a detailed flow chart on the management of hypersensitivity reactions. All of the nurses are fully insured with Professional Indemnity insurance and as such meet the criteria to practice in this environment. All infusion centres are equipped with, at a minimum, an IV pole, infusion pump, a size C oxygen cylinder with regulator/flow meter and a suitable infusion chair or bed. All dispensables and emergency drugs are brought with the registered nurse to each infusion."

The sponsor also indicated that all nurses carry an emergency box which includes appropriate medicines for use in the event of a hypersensitivity reaction and that additionally, each infusion centre is equipped with an appropriate emergency kit.

"During infusions, nurses have a one-to-one relationship with the patient throughout the entire infusion. A basic medical assessment/medical history check is conducted prior to each infusion to determine that the patient has not previously experienced a hypersensitivity reaction to Actemra and is fit to receive the infusion. Observations taken include blood pressure, pulse and temperature. These are taken, at a minimum, prior to the infusion, 30 minutes into the infusion, and approximately 5 minutes post infusion. Observations may also be taken during the first 15 minutes to further assess any signs of hypersensitivity."

The committee agreed that risk minimisation strategies should focus on measures to avoid subsequent infusions in patients with signs of hypersensitivity to a previous infusion, or, that if further infusion was attempted in patients with possible hypersensitivity previously, that this be done only under medical supervision and with full resuscitation facilities.

The sponsor provided the following response to this advice:

"As per the current approved PI rechallenge of a patient with Actemra after a previous known or possible hypersensitivity reaction is contraindicated. Patients with a history of any reaction consistent with hypersensitivity to any component of the medicine must not be re-challenged with Actemra.

Prior to receiving an infusion in an infusion centre each patient undergoes a basic medical assessment/medical history check to determine that he/she has not previously experienced a hypersensitivity reaction to Actemra and is fit to receive the infusion. If the patient has suffered a previous reaction then he/she will not be allowed to receive Actemra under the ACTiv program. Should the prescriber wish to pursue use of Actemra, the only other way to access the medicine would be in the hospital setting, and therefore administration would be attempted under medical supervision in a hospital with full resuscitation facilities.

Given the contraindicated nature of rechallenge the sponsor does not consider the suggestion to be practical within the scope of the ACTiv program and does not intend to implement it in this setting."

Additionally, ACSOM felt that the protocol guidance in place for the infusion centres should indicate a recommended time interval for post-infusion patient observation. The committee agreed that an appropriate post-infusion observation time of 15 minutes would be acceptable (extended to 30 minutes if practical).

The sponsor proposed to update the Actemra PI and educational materials to include a reference to a 15 minute post-infusion observation period.

The OPR reviewer noted that the information provided by the sponsor demonstrates that infusion nurses undergo extensive training and the sponsor and its partner have training and protocols in place for recognising and managing hypersensitivity reactions. The training course is specifically focused on severe allergic reactions and anaphylaxis. Given the concerns of the Delegate and the ACPM regarding anaphylaxis, it was considered that the course may satisfy the advice provided by ACSOM. However, it was recommended that the sponsor provide evidence of the validity of the training course, such as details of the course accreditation.

Regarding ACSOM's advice that infusion centre staff have immediate access to a medical officer, OPR was satisfied that sufficient risk minimisation measures are in place and a medical officer is not required to be present, as long as an acceptable safety protocol can be finalised.

Finally, upon review of the documents and information provided by the sponsor, it was apparent that ACSOM's advice that risk minimisation should focus on avoiding subsequent infusions, has already been incorporated into current practices. Patients are counselled prior to infusion and those who have had a previous hypersensitivity reaction will be referred back to their prescribing physician.

Summary of recommendations

The OPR reviewer provided the following recommendations to the Delegate:

- That the Australian RMP version 1 to be updated as per the sponsor's commitments and that the updated RMP be imposed as a condition of registration.
- That the safety protocol 'Standard Operating Protocols: Actemra Intravenous Infusion Program' and the Infusion booklet 'Step-by-step infusion instructions for Actemra' (and any other relevant educational materials) be updated to include a 15 minute post-infusion observation period.
- Prior to finalising the safety protocol:
  - the sponsor provide an updated version of the protocol following consultation with ANZCA and which includes their feedback.
  - the sponsor provide evidence that the anaphylaxis protocol included as part of the safety protocol is consistent with the Therapeutic Guidelines: Emergency Medicine and/or the ARC guidelines for the management of anaphylaxis.
  - the Delegate consider the questions raised by the OPR concerning the safety protocol
- Regarding ACSOM's advice that infusion centre staff have immediate access to a medical officer, OPR was satisfied that sufficient risk minimisation measures are in place and a medical officer is not required to be present as long as an acceptable safety protocol can be finalised. In the event that the safety protocol is not finalised to the satisfaction of the Delegate, it was recommended that ACSOM's advice be revisited.
- That the sponsor provides evidence of the validity of the training course on recognising and treating anaphylaxis, such as details of the course accreditation.
- The sponsor to be required to inform the TGA if sJIA infusions will occur in infusion centres. If so, the sponsor will be required to provide OMA and OPR with a justification for this decision which specifically addresses the additional concerns associated with administering Actemra in a vulnerable paediatric population.

- The Delegate consider the clinical evaluation report as it addresses the risk of infection and determine if there is a need to consult with OPR regarding the need for additional risk minimisation activities to mitigate and communicate this risk.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

New GLP compliant developmental toxicity studies were conducted in juvenile mice, which were administered IV infusions of the murine analog of tocilizumab, MR16-1 from PND 22 to PND 79. These studies bridged the gap between the previously evaluated pre/postnatal studies with MR16-1 in mice and previously evaluated studies with tocilizumab in adolescent and adult monkeys.

New toxicokinetic data and previous pharmacodynamic data showed that the dosing schedules of 15 or 50 mg/kg MR16-1 every 3 days in mice achieved steady state levels and maximal pharmacological efficacy over the treatment period from weaning to sexual maturity. The nonclinical evaluation report did not make any comment on the issue of exposures in rodents relative to exposures in humans. The Delegate checked with the toxicology evaluator on this point and was told that, from a strictly scientific point of view, the nonclinical data could not be used for this purpose. This was because tocilizumab and its murine analog, MR16-1, were different molecules. *The sponsor was invited to make a comment on this issue.*

There was no evidence of reduced exposure due to anti-MR16-1 antibody formation. MR16-1 was cleared from the circulation by 50 days after the last dose.

General toxicity observations were limited to decreased monocyte counts, minor changes in serum glucose and serum globulins and increased thyroid weights in males. These effects were partially or fully reversible and were not toxicologically significant. There was no significant suppression of neutrophils or of platelets or elevation in hepatic transaminases as has been observed in clinical trials of tocilizumab in children.

Sexual maturation and skeletal development were unaffected by MR16-1.

Immunophenotyping showed small but significant changes in lymphocyte subsets after MR16-1 treatment. However, these changes did not result in any functional impairment of the immune system.

There were no nonclinical objections to the registration of tocilizumab for the proposed extension of indication.

Clinical

Clinical evaluation

The application for extension of indication in sJIA was supported by data from the pivotal study WA18221 (the TENDER study) and a number of supportive studies.

The clinical evaluator has recommended that tocilizumab (Actemra) should be approved for the indication:

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

Pharmacology

The pharmacokinetic data were from the population pharmacokinetic study conducted as part of a larger study, WA18221 which was a 12 week, randomised, double blind, placebo controlled, parallel group, two arm study to evaluate the efficacy and safety of tocilizumab in patients with active sJIA. In the initial clinical evaluation, the clinical evaluator found that the population PK study was not described in sufficient detail and therefore asked a number of questions of the sponsor.

The structural PK model was a two compartment model with concurrent saturable and non-saturable elimination pathways and was based on prior data and analyses from an adult population, these data and analyses having not been provided in the report. The estimates of the PK parameters and error terms are presented in Table 6. As noted by the clinical evaluator, the data collected, consisting of two point data (peak and trough) would have been suitable for estimating the parameters for a one compartment first order elimination model but were unsuitable for the estimation of a two compartment, combined first order and Michaelis-Menten elimination model. A considerable proportion of the data should have been mid-dose, in addition to peak and trough, to enable estimation of such a model. In addition, clearance was assumed to be a constant parameter whereas if there is any component of Michaelis-Menten elimination then clearance cannot be a constant (nor can half-life). However, the clinical evaluator was of the opinion that the analysis might still be able to provide an estimate of the effects of body size and age upon volume of distribution and total clearance. Half-life might then be calculated as a secondary parameter from volume of distribution and clearance.

Clearance was calculated as approximately 8 mL/h and half-life as 19 days, both values consistent with the information in the PI. The clinical evaluator concluded that the population PK analysis was adequate.

There were some PD data reported in WA18221. The increases in serum concentrations of IL-6 and sIL-6R were consistent with the proposed mechanism of action of tocilizumab. Response to tocilizumab did not appear to be related to the magnitude of tocilizumab exposure.

Efficacy

Efficacy data were presented from one placebo controlled study of 12 weeks duration (WA18221) and one combined long term, open label follow up study (MRA317JP/MRA324JP).

Study WA18221

WA 18221 was a 12 week randomised, double blind, placebo controlled, parallel group, two arm study to evaluate the efficacy and safety of tocilizumab in patients with active sJIA (Part 1). The study had a 92 week single arm, open label extension (Part 2), followed by a 3 year open label continuation (Part 3). The study was conducted at 43 centres in 17 countries. Only the data from the 12 week randomised, double blind phase were included in the study report.

The primary efficacy outcome measure was the proportion of subjects with at least 30% improvement in JIA ACR30 response at week 12 and absence of fever. There were 23 secondary endpoints.

For the primary efficacy outcome variable, there were a higher proportion of responders in the combined tocilizumab group than the placebo, $p < 0.0001$. The results are shown in Table 1.

All 23 secondary endpoint results were statistically significant, $p < 0.05$.

The logistic regression analysis of ACR30 response indicated a significant effect for MTX use, with a reduction in the odds of response associated with MTX use: OR [95% CI] = 0.23 [0.05, 0.94], p = 0.0414. However, despite this, there did not appear to be a clinically significant difference in efficacy between those subjects treated with MTX at baseline and those not. The Delegate noted that the proportions of those who achieved the primary efficacy endpoint were comparable in the tocilizumab treated groups, regardless of whether the subjects were on methotrexate at baseline or not. However, in the placebo group, 45.5% (5/11) of subjects not on methotrexate at baseline achieved the primary endpoint while 15.4% (4/26) of subjects who were on methotrexate at baseline achieved the primary endpoint. In addition, there is broad comparability between the Week 6 and Week 12 results in all groups except for the placebo group not on methotrexate at baseline. In this group the number and percentage of primary endpoint responders rose from 18.2% (2/11) to 5/11 (45.5%). The Delegate noted that these results appeared counter-intuitive, at least with regard to the role of methotrexate in the treatment of sJIA. *The sponsor was invited to comment on this observation.*

The sponsor was also asked whether subjects were able to be either withdrawn from or commenced on methotrexate during the 12 week double blind period. If either was permitted, were there any data which show how such strategies may have affected the efficacy endpoints?

When analysed by age category (2 to 5 years, 6 to 12 years and 13 to 18 years), there was similar efficacy for each of these age groups with efficacy on tocilizumab being consistently better than on placebo.

Study MRA317JP/MRA324JP

Study MRA317JP/MRA324JP was a combined report of the long term follow up data from Studies MRA011JP, MRA317JP, MRA316JP and MRA324JP. All of these studies were conducted in Japan. Across the studies there were 149 subjects enrolled and treated. It would appear that a total of 114-118 subjects entered the extension phases of these trials. For those subjects who remained in the study, response rates were maintained for up to 324 weeks. Response rates at selected time points were as follows: Week 12, 85/114 (74.6%), Week 24, 98/118 (83.1%), Week 48, 91/106 (86.7%), Week 96, 69/74 (93.2%) and Week 192, 29/32 (90.6%). From Week 228 onwards, numbers of subjects remaining are down to single digit figures. At Week 324, the response rate is 100%, from 8/8 subjects.

Clarifications of the efficacy data sought by the clinical evaluator for the Round 2 assessment

Some long term efficacy data from Study WA18221, the pivotal study, was provided in the *Summary of Clinical Efficacy*. A total of 112 subjects were treated with tocilizumab in Part 2 of the study and 50 of these were exposed for one year or more. Of these 112 subjects, 78 (69.6%) had previous or ongoing MTX use. For the primary efficacy outcome measure, JIA ACR30 response with absence of fever, 50 of the subjects treated at week 60 had achieved this outcome. According to the clinical evaluator, the latter group of 50 represented 89.3% of the subjects treated at Week 60 which implies that the denominator, or the total number of all subjects treated at Week 60, is equal to 56. The clinical evaluator goes on to say that response was maintained for up to 72 weeks. However, the value of

the denominator used to generate the percentage of responders at each time point along the horizontal axis was not clear from Figure 8. The same problem occurs with Figure 9, which shows the proportion of patients achieving a JIA ACR90 response at visits up to Week 72 in WA18221.

The sponsor was requested to display both figures amended to show the total number of patients eligible for assessment at each of the time points shown. The Delegate also requested that the sponsor state the number and percentage of subjects (out of the 50 who were exposed for one year or more) who were still achieving the primary efficacy endpoint at their last assessment.

It appeared that the only data evaluated so far for the purpose of long term efficacy has been that from Study MRA317JP/MRA324JP which was in turn a combined report of the long term follow up data from Studies MRA011JP, MRA317JP, MRA316JP and MRA324JP. *The sponsor was requested to confirm that this is the case and that there is no overlap between the subjects enrolled in any of these studies and in the pivotal study, WA18221*.

The sponsor was also asked to comment on the effect on outcomes of concomitant treatment with MTX and tocilizumab in the Japanese clinical trials MRA317JP/MRA324JP. For the latter, treatment with MTX was an exclusion criterion and so any effect of concomitant treatment could not be determined in these studies.

Safety

Safety data were presented from the two studies, the pivotal study WA18221 and the studies conducted in Japan, MRA317JP/MRA324JP. In the former, the median exposure to study medication was 12.14 weeks while in the latter 149 subjects were exposed to tocilizumab for a median duration of 2.1 years. However, the numbers of patients who were or have been exposed to tocilizumab, firstly for 6 months and secondly for 12 months, in each of these studies were unclear. *The sponsor was requested to provide these data.*

Overall, adverse events were more frequent in subjects treated with tocilizumab, particularly infective AEs. In the pivotal study, WA18221, there were 21 infection related AEs reported in 18 (48.6%) subjects in the 8 mg/kg group, 34 in 23 (60.5%) in the 12 mg/kg group and 14 in 11 (29.7%) in the placebo group. Infective AEs were more common in tocilizumab groups in general, with a range of different types of infection involved. The rate of infectious AEs increased with dose. The rate of gastrointestinal AEs was greater in the tocilizumab groups, particularly diarrhoea and vomiting. Likewise in the Japanese studies, the most commonly reported AEs were infections, reported in 135 (90.6%) subjects. Infusion reactions were another important category of AEs.

In the pivotal study there were 3 SAEs (2 infection related, one of which was bacterial arthritis and one angioedema/urticaria) in the tocilizumab groups versus none in the placebo group. There were no deaths. In the Japanese studies, there were 105 SAEs reported in 62 (41.6%) subjects with the most commonly reported being infection related in 29 (19.5%) subjects. There were 2 deaths in the Japanese studies, one as a result of histiocytosis haematophagic (macrophage activation) syndrome and one due to amyloidosis.

Elevation of ALT and AST was more common in patients treated with tocilizumab but this did not appear to be translated into an increased incidence of liver disease. Increased serum cholesterol was also reported in a small number of subjects. In the Japanese studies, decreased lymphocyte count was reported in 25 (16.8%) subjects and decreased neutrophil count in 18 (12.1%).

In the pivotal study, one subject developed neutralising antibodies by Week 12. Urticaria and angioedema were more common in the tocilizumab groups. In the Japanese studies, immune system disorders were reported in 13 (8.7%) subjects while anaphylactic reaction was reported in 2 (1.3%) subjects and drug hypersensitivity in one (0.7%).

Clarifications of the safety data sought by the clinical evaluator for the Round 2 assessment

In the long term safety data which was available for the pivotal study, WA18221, there were 112 children exposed to tocilizumab with 50 exposed for greater than one year. The total duration of observation was 132.4 patient years. There were 32 SAEs in 25 (22.3%) subjects, including 3 (2.7%) with haemophagocytic histiocytosis, 3 (2.7%) with varicella and 3 (2.7%) with gastroenteritis. There was one death from tension pneumothorax in a 16 year old male. Neutropenia was reported in 20 (17.9%) subjects and one subject had an abnormally low platelet count while 13 (11.6%) had ALT elevations. There were 11 infusion related events in 9 subjects.

Postmarketing data

There was no specific postmarketing data in the paediatric population available for evaluation by the clinical evaluator.

The sponsor was requested to provide brief summaries of all cases in the Immune System Disorders SOC, together with outcomes, occurring in children receiving tocilizumab and known to the sponsor in its global safety database.

No case reports were received during this reporting period concerning the use of tocilizumab in neonates or infants during this reporting period. A total of 44 case reports (comprising 112 AEs) were received from 42 patients in the child and adolescent population. Of the 112 reported AEs, 64 were classified serious. The majority of SAEs were reported in *Infections and Infestations* (12 SAEs, 18.8%), followed by *General Disorders and Administration Site Conditions* (8 SAEs, 12.5%). The most frequently reported SAEs were pneumonia (3 SAEs) and juvenile arthritis (3 SAEs). One case involving a child and one involving an adolescent patient had fatal outcomes:

The sponsor was requested to provide a narrative for the case involving the death of a 2 year old patient. The sponsor was also requested to provide brief summaries of all fatal cases occurring in children receiving tocilizumab and known to the sponsor in its global safety database.

Other important safety information

On 27 April 2011, the sponsor notified the TGA of a suspected adverse drug reaction report of an unexplained death in a 6 year old patient in relation to study WA18221.

Six months after commencement of IV infusions of blinded tocilizumab once every 2 weeks as a participant in study WA18221 (and subsequently entered the open label extension arm of the study), the patient experienced vomiting. He was otherwise well with no fever. The following day he was lethargic and was being taken to hospital but fell unconscious on the way and died. The investigator assessed the event of death-unexplained to be related to the patient's pre-existing/underlying disease systemic arthritis, tocilizumab, other treatment of methotrexate and other-possible gastroenteritis.

On 21 April 2011, the Roche Safety Database was searched for tocilizumab cases for all indications with the MedDRA preferred terms of death and sudden death. Among the 52 previous cases, 38 were clinical trial reports, 13 were spontaneous cases with 10 male, 25 female and 17 with gender not reported. The age range was from 1 to 83 years. Causality

was assessed as related to tocilizumab in 11 patients, unrelated in 13 patients and unknown/not reported in 10 patients.

The sponsor was requested to comment on whether there were any features in common to the 11 cases in which causality was assessed as related to tocilizumab.

An updated report was submitted by the sponsor to the TGA. An autopsy was performed. The direct cause of the death was reported as septicaemia and "other significant condition contributing to the death but not relating to the disease or condition causing it" was juvenile rheumatoid arthritis (Still's disease). The autopsy examination also showed psoriasis type changes of the nails and microscopic examination of tissue samples also supported a diagnosis of septicaemia. Old right lung adhesions were also revealed and blood cultures were positive. The investigator assessed the event of death to be related to pre-existing /underlying disease, condition systemic arthritis, tocilizumab, other treatment of methotrexate and other-possible gastroenteritis.

Risk Management Plan

Safety specification and pharmacovigilance plan

The clinical evaluator was of the opinion that a potential risk which has not been identified by the sponsor is vaccination (lack of effect). *The sponsor was requested to comment on this issue.*

The 5 specific conditions of registration imposed by the Delegate with the approval of the previous submission are shown on page 37 of this AusPAR.

As per the first specific condition of registration, the issue of the appropriate location for the IV infusions of tocilizumab was referred to the sixth meeting of ACSOM held on 11 March 2011. ACSOM shared the concerns of the ACPM about the capability of infusion centres to respond to serious hypersensitivity reactions and anaphylaxis. ACSOM recognised that it may not be practical to administer infusions in a hospital setting and suggested a number of measures which could be considered to support prompt and appropriate patient management in the event of a serious hypersensitivity reaction or anaphylaxis.

ACSOM felt that continuing education and training should include, in particular, training in the recognition of hypersensitivity so that future administration of tocilizumab could be avoided, as well as training in recognising severe hypersensitivity and patient deterioration so that such events could be promptly managed.

The summary of the ongoing safety concerns in paediatric patients as specified by the sponsor is outlined in Table 8 of this AusPAR. While this table is shorter than the corresponding table for adults, the sponsor explained that this was to characterise the particular concerns for the sJIA indication and paediatric patients which were raised by the EU CHMP. The OPR evaluator was satisfied with the sponsor's justification and concluded that, for the purposes of this evaluation, the ongoing safety concerns in adults are also considered to be ongoing safety concerns in children. The summary of ongoing safety concerns provided by the sponsor includes serious infections and serious hypersensitivity reactions as important identified risks in adults and children.

The sponsor's detailed justification for the use of international registries and the assurance that the data from these registries is applicable to the Australian population was accepted by the OPR evaluator as were the sponsor's justifications and evaluation of the need for risk minimisation activities. The sponsor's discussion of the potential for medication errors associated with both the RA and the sJIA dosage regimens was found to be acceptable.

Risk Minimisation

The OPR evaluator assessed the risk minimisation plan and made the following comments with regard to the proposed educational campaign:

- The sponsor has committed to updating the educational materials to include a 15 minute post-infusion observation period.
- There was no objection to the sponsor implementing the educational program as outlined for the RA indication. However, additional comments were made on the safety protocol and included some observations for the Delegate's consideration

With regards to the education program for the sJIA indication, the sponsor stated that they are "currently evaluating whether to utilise infusion centres for patients with sJIA. The infusion centres have been set up to facilitate access to the medication for RA patients who would otherwise be unable to obtain treatment in the hospital setting. It is expected that the number of patients to be treated for sJIA will be low and consequently there will be limited requirement to use the infusion centres."

Upon making a decision as to whether to use the infusion centres for patients with sJIA, the sponsor should be required to inform the TGA of their decision. If the sponsor intends to use the infusion centres for patients with sJIA, they should be required to provide OMA and OPR with a justification for this decision which specifically addresses the additional concerns associated with administering Actemra in a vulnerable paediatric population.

With regard to the issue of whether or not to use infusion centres for patients with sJIA, the Delegate was inclined to recommend that all children with sJIA be administered tocilizumab within a hospital setting with immediate access to medically qualified personnel. The Delegate's chief concerns here are the very particular requirements of children with regard to administration of IV fluids. These concerns become even more critical, the younger the child. *The Delegate requested the advice of the ACPM on this particular issue.*

The last three specific conditions of registration all relate to the risk minimisation plan and with regard to the sponsor's proposed strategies in response to those conditions, the OPR evaluator made the following comments:

- The OPR evaluator noted that the sponsor has had some success in liaising with expert organisations and was reassured that the safety protocol has been developed with expert consultation and input.
- The OPR evaluator did not evaluate the clinical components of the safety protocol, rather it has been reviewed to ensure consistency with all of the information the sponsor has provided regarding Actemra infusions in the RA indication.
- As per ACSOM's advice and in order to ensure consistency, the OPR evaluator recommended that the sponsor be required to update the protocols to include the need for a 15 minute post-infusion observation period. The ACSOM thought that the latter should be extended to 30 minutes if practical.
- In addition, to ensure uniformity of the sponsor's proposed protocol with current clinical guidelines, the OPR evaluator recommended that the sponsor be required to provide evidence that the anaphylaxis protocol included as part of the safety protocol is consistent with the Therapeutic Guidelines: Emergency Medicine and/or the ARC guidelines for the management of anaphylaxis.
- The OPR provided observations/comments for the Delegate's consideration regarding the safety protocol.

The Delegate responded that whatever protocols are devised they should be in accord with best practice clinical guidelines. In the opinion of the Delegate and regarding the emergency management of anaphylaxis, the most useful are those guidelines issued to Australian doctors very recently by the *Australian Prescriber*.[14] These guidelines have been endorsed by the Australasian Society of Clinical Immunology and Allergy, the Royal Australasian College of Physicians, the Royal Australian College of General Practitioners, the Australasian College for Emergency Medicine, the Royal Australian and New Zealand College of Radiologists, the Internal Medicine Society of Australia and New Zealand and the Australian Dental Association. A registered nurse should have the professional competence to undertake the first 4 out of the total of 7 steps recommended in the guidelines (+ the administration of salbutamol by spacer or nebulizer if appropriate). The protocols should also take note of the new Australian Resuscitation Guidelines.

Advice was obtained from the ACSOM regarding the extent to which resuscitation facilities should be required during administration of Actemra to a patient. The OPR reviewer had the following comments to make:

- While ACSOM recommended nurses be trained in the program 'Recognising and Responding to Clinical Deterioration' provided by the Australian Commission on Safety and Quality in Health Care (ACSQHC), the sponsor's partner provides their own course to nurses.
- The information provided by the sponsor demonstrates that infusion nurses undergo extensive training and the sponsor and its partner have training and protocols in place for recognising and managing hypersensitivity reactions. The training course is specifically focused on severe allergic reactions and anaphylaxis. Given the concerns of the Delegate and the ACPM regarding anaphylaxis, it is considered that the course may satisfy the advice provided by ACSOM. However, it is recommended that the sponsor provide evidence of the validity of the training course, such as details of the course accreditation.
- Regarding ACSOM's advice that infusion centre staff have immediate access to a medical officer, OPR was satisfied that sufficient risk minimisation measures are in place and a medical officer is not required to be present, as long as an acceptable safety protocol can be finalised.
- Finally, upon review of the documents and information provided by the sponsor, it was apparent that ACSOM's advice, that risk minimisation should focus on avoiding subsequent infusions, has already been incorporated into current practices. Patients are counselled prior to infusion and those who have had a previous hypersensitivity reaction will be referred back to their prescribing physician.

The Delegate noted the recommendations of the OPR reviewer to the Delegate (see pages 40-41).

The Delegate mostly agreed with the recommendations. However, given the use of an IV infusion of a biological product foreign to the human immune system, the Delegate would be more reassured by the institution of a 30 minute post-infusion observation period. The Delegate has expressed his views concerning the particular guidelines which should be taken into account in the drawing up of the protocol for safe administration of tocilizumab and his concerns that the provision of injectable promethazine and hydrocortisone may represent unhelpful distractions for the nurse in an emergency situation. Also, as the Delegate has already indicated, he was inclined to recommend that infusions for the

[14] Anaphylaxis: emergency management for health professionals. Aust Prescr 2011; 34: insert. Available at http://www.australianprescriber.com/upload/issue_files/3404_wallchart_2011.pdf

paediatric indication of sJIA should only take place in hospitals with immediate access to medical personnel. The Delegate was also inclined to recommend some specific conditions of registration relating to enhanced or heightened pharmacovigilance activities with respect to the paediatric sJIA indication.

Risk-Benefit Analysis

Delegate Considerations

Efficacy

Study WA18221 demonstrated efficacy for tocilizumab in children and adolescents with sJIA over a 12 week period. Study subjects did have marked improvement in all parameters, both primary and secondary. There was no apparent difference in efficacy between subjects treated concomitantly with MTX and those who were not. Nor did corticosteroid dose appear to influence efficacy. Efficacy appeared to be maintained for up to 72 weeks and was demonstrated for each of the age groupings: 2-5 years, 6-12 years and 13-18 years.

Study MRA317JP/MRA324JP showed some evidence for the persistence of efficacy for up to 324 weeks although by this time, the numbers of assessable subjects were very small. However, persistence of efficacy was demonstrated in reasonable numbers up to about Week 168. The clinical evaluator also made the valid point that these data were uncontrolled.

Safety

Overall, AEs were more frequent in subjects treated with tocilizumab, particularly infective AEs. The risk of all types of infection was increased, including both serious infections and infections leading to death. The risk increases with dose. There is the issue of the death of the 6 year old boy in an extension phase of the pivotal study from septicaemia and the precise contributors to the latter. The SAEs reported in the pivotal study were either infective or immunologically mediated. In MRA317JP/MRA324JP the most commonly reported group of SAEs was infective. It was not clear the extent to which the risks of AEs and infections in particular are increased by concomitant treatment with MTX.

Macrophage activation syndrome, resulting in death was reported in one subject in Study MRA317JP/MRA324JP. Haemophagocytic histiocytosis was reported in 3 subjects during the extension to Study WA18221.

The terms macrophage activation syndrome and haemophagocytic histiocytosis appear to be used interchangeably at times. The sponsor was requested to clarify the precise relationship between these two conditions.

Elevations in ALT and AST were more common in subjects treated with tocilizumab but this did not appear to be translated into an increased incidence of liver disease. Increased serum cholesterol and decreased lymphocyte and neutrophil counts were also observed. Urticaria, angioedema and anaphylaxis were also reported.

Protocol for safe administration of tocilizumab

The Delegate was satisfied with the way the sponsor has approached the task of producing a high quality protocol aimed at providing for the safest possible setting for the administration of tocilizumab. The Delegate reiterated that any such protocols should be very consistent with accepted best practice guidelines such as those published in the *Australian Prescriber* and the new Australian Resuscitation guidelines. These guidelines are being drawn up to aid registered nurses and therefore the Delegate would be more

reassured by the institution of a 30 minute post-infusion observation period, by the withdrawal of both the injectable promethazine and hydrocortisone from the protocol as they are potentially hazardous distractions and by the location in hospitals of tocilizumab infusions for the paediatric indication of sJIA, at least initially.

The Delegate proposed to approve the submission for the extension of indication as follows:

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

The Delegate proposed the following specific conditions of registration:

- The implementation of the latest version of the Australian specific Risk Management Plan, version 1.
- The provision of the final study reports of the ongoing studies WA18221 and WA19977 as evaluable data within the context of category 1 submission(s).
- That administration of tocilizumab for the paediatric indication of sJIA should take place in a hospital with immediate access to medical personnel, at least until there is adequate demonstration of safety of administration in sufficiently large numbers of children
- Enhanced pharmacovigilance monitoring of all serious infections, serious anaphylactic reactions, serious anaphylactoid reactions, serious hypersensitivity reactions and deaths in children receiving tocilizumab for sJIA (or for any other indication) in the form of regular, specific updates, separate from PSURs, to be submitted to the OPR every 3 months for a period of 24 months from the date of approval of the submission. Any deaths are to be notified to the TGA as soon as possible after the event.

In addition to the questions directed to the sponsor and the question to ACPM with regard to the special requirements of children, the Delegate asked the ACPM three other questions:

1. Does the ACPM agree that the population PK analysis is adequate for determining the PK parameters reported in the PI for children?
2. Does the ACPM agree with the Delegate that the provision of injectable promethazine and hydrocortisone within the protocol for emergency management of anaphylaxis is a potentially hazardous distraction for the nurse involved in that emergency management?
3. Does the ACPM endorse the specific conditions of registration proposed by the Delegate?

Response from sponsor

The sponsor noted that the Delegate recommended the following indication for approval:

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

The sponsor concurred with the Delegate's recommended indication and addressed the issues raised by the Delegate.

Adequacy of the population PK analysis

The sponsor provided a detailed response to this question.

Emergency management of anaphylaxis

The sponsor acknowledged the Delegate's comments and the recommendations published by the Australian Prescriber.[14] The sponsor would prefer promethazine remain a treatment option in the mild to moderate symptoms arm of the protocol since it is accepted therapy for the treatment of allergic reactions. Similarly for the severe symptoms arm the sponsor would prefer hydrocortisone remain a treatment option because of the role it can play in the treatment of biphasic anaphylaxis and bronchospasm. The sponsor also pointed out that nurses following the protocol would, after stopping drug administration, always give adrenaline prior to any other action, including administration of promethazine and hydrocortisone. The step by step nature of the protocol ensures a single nurse should be able to manage subsequent steps without them becoming unhelpful distractions.

Delegate's proposed specific conditions of registration

The first two proposals by the Delegate were acceptable to the sponsor.

The sponsor did not oppose the Delegate's proposed condition of registration that administration of tocilizumab (TCZ) for the paediatric indication of sJIA should take place in a hospital with immediate access to medical personnel, at least until there is adequate demonstration of safety of administration in sufficiently large numbers of children. The sponsor requested the opportunity to revisit this condition of registration in the future based upon accumulated safety data from the paediatric population.

The sponsor believed there will be circumstances in the future where the use of infusion centres may improve the quality of treatment provided to sJIA patients.

With regard to enhanced pharmacovigilance monitoring, the sponsor suggested an alternative option. The information requested (all serious infections, serious anaphylactic reactions, serious anaphylactoid reactions, serious hypersensitivity reactions and deaths in children receiving TCZ for sJIA or any other indication) is currently included in the PSURs which are provided to the TGA via the 6 monthly reporting cycle. The sponsor proposed to supplement the PSURs by provision of two additional 3 monthly reports during the intervening periods between PSURs. The sponsor acknowledged this is a slightly different format to the Delegate's proposed action; however under the sponsor's plan the TGA would still receive the necessary information in the same timeframes as proposed by the Delegate.

Nonclinical data

The sponsor agreed that it is correct that animal safety data using surrogate antibodies are generally not suitable to be used in exposure comparisons and safety margins calculations. However, together with disease relevant pharmacological data, generic statements relevant to the biology of IL-6 blockage can be made. In this context, pharmacology data on MR16-1, the surrogate antibody to TCZ used for the juvenile toxicity study in the mouse, indicate that this study was conducted at exposures considerably above full inhibition of IL-6R blockage. Hence, the study does fulfil criteria for safety assessment for biological consequences of IL-6R blockage in the juvenile state although MR16-1 and TCZ are different molecules. As for biologics in general, off target effects other than those mediated by blockage of the target (IL-6) are not expected.

Withdrawal from or commencement on methotrexate

As outlined in the study protocol, for those patients receiving background methotrexate (MTX) at baseline the dose could be decreased for documented reasons of safety but not for efficacy (improvement in symptoms) in the Part I (12 week double blind period) of

study WA18221. For patients not receiving background MTX, treatment could not be commenced in Part I of the study unless required for a safety reason but there were no occurrences of this in the study. Stability in dosing was required in the 8 week period prior to the baseline visit and during Part I of the study. An option to discontinue, or reduce (or commence) MTX dosing was available in the event of a safety concern. In the 12 week double blind period, 1 placebo patient stopped MTX treatment, 2 TCZ patients stopped MTX treatment and 3 TCZ patients reduced their MTX dose. These MTX dose changes were not accounted for in the pre-planned analyses of efficacy endpoints. Due to the low number of patients involved, the influence on results would have been minimal. The values quoted in the Delegate's rationale are from a secondary efficacy endpoint analysis which included a covariate of modifications (unchanged, increased, decreased, stopped) in oral corticosteroid dose. A separate analysis involved solely the treatment groups and the 4 stratification variables used in randomisation. Within this analysis, the odds of response associated with background MTX use, while still reduced, were not significant: OR [95% CI] = 0.38 [0.10,1.45], p = 0.1551. The Table arises from a subgroup analysis of key efficacy responses by background MTX use at baseline. Stratification by MTX was included in the randomisation at baseline in Part I of the study and TCZ patients receiving background MTX might be expected to respond better than those not receiving background MTX. These results show this not to be the case and are consistent with a published study which highlighted the limited effectiveness of MTX on the systemic features of sJIA.[15] The response rates amongst placebo patients not on background MTX do improve over time, with an additional 3 patients achieving the primary endpoint at Week 12. However the subgroup not receiving background MTX that were assigned to placebo is very small, with each patient contributing 9% (1/11) to the overall response and as such differences should be interpreted with caution. A hypothetical explanation would be that MTX is more likely to be prescribed in patients with consistently active disease and therefore these patients are less likely to show regression to the mean. However there are no longitudinal baseline disease activity data available to support this. As discussed by the Delegate, the key findings of this subgroup analysis are the comparable efficacy responses achieved in the TCZ group regardless of background MTX use or non-use.

Display of figures and number and percentage of subjects who were exposed for one year or more, who were still achieving the primary efficacy endpoint

The sponsor provided the figures requested. The associated tables and highlight the numerators and denominators involved in the calculation of the percentage response at each of the plotted time points. Given the need to provide a prompt response, inclusion of the denominators on these clinical trial report graphical displays was not possible. However, the number of patients included, at the major axis time points are: baseline (n=112), Week 12 (n=110), Week 24 (n=109), Week 36 (n=108), Week 48 (n=95), Week 60 (n=56) and Week 72 (n=33). These are applicable to both figures. The denominator at each visit is the number of patients that reached the time point at the data cut, with withdrawn patients being excluded at post-withdrawal visits. The long term efficacy data for WA18221 is provided from a reporting event data cut on 10 May 2010 and includes all patient data up to and including this date, by this time point at least 50 patients were treated on TCZ for at least 1 year in Part II of the study.

Thus there was additional exposure on TCZ from Part I of the study, including the patients randomised to TCZ and the patients randomised to placebo that escaped to open label TCZ therapy. Based on patient listings, up to the time of the data cut, 85 patients (75.9%) were exposed to TCZ for at least 1 year. Of these 85 patients, 79 (92.9%) achieved the primary

[15] Woo P et al. Randomized, placebo controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheumatism 2000; 43: 1849-1857.

endpoint (JIA ACR30 response + absence of fever) at their last completed assessment prior to the data cut. Of note, this would be at patient specific time points based on date of first dose of TCZ with some exposure variation in terms of the latest visit reached.

These data were not included as part of the CSR, which only focuses on Part I of study WA18221. The completed Part II CSR will be provided separately in due course.

Lack of overlap

The submission focuses on Part I of study WA18221. It does not contain any data from Part II of WA18221. Part II data will be provided in a separate CSR in due course. The long term data proposed for the label is supported by the efficacy and safety data cut taken on 10 May 2010 of the patients reaching treatment with TCZ for a minimum of 1 year in Part II of study WA18221. This was provided in the submission.

Data from the Chugai studies were included in the submission as supportive data. There is no overlap between the subjects enrolled in any of the Chugai studies and study WA18221.

Exposure to tocilizumab

The long term efficacy and safety data for WA18221 is provided from the reporting event data cut on 10 May 2010 and includes all patient data up to and including this date; by this time point at least 50 patients were treated on TCZ for at least 1 year in Part II of the study. Exposure to TCZ (years) was calculated as: (date of last TCZ infusion - date of first TCZ infusion + 15)/365.25. An addition of 14 days was allowed, to account for washout of active drug from the body system. An additional day (+1) is included within the calculation of exposure as standard to allow for the fact that infusions are given on the first and last dates provided.

Based on the patient listings to 10 May 2010 109/112 (97.3%) patients were exposed to TCZ for at least 6 months and 85/112 (75.9%) patients were exposed to TCZ for at least 12 months. For the studies conducted in Japan, a total of 149 patients received TCZ, across the 2 long term studies MRA317JP and MRA324JP. Study MRA317JP was an optional extension study for those who were enrolled into studies MRA011JP and MRA316JP. Study MRA324JP was an additional long term study for new patients. Based on the study day of last infusion and applying the same methodology as used in TENDER (addition of 14 days to duration of exposure) the following results are obtained: 124/149 (83.2%) patients were exposed to TCZ for at least 6 months and 106/149 (71.1%) patients were exposed to TCZ for at least 12 months.

Cases in the Immune System Disorders SOC

A search of the Global Safety Database was performed on 31 August 2011, with a data cut-off date of 26 August 2011. The search included all events that were coded to *Immune System Disorders* and reported in patients who were under 18 years of age. Overall, there were 13 events identified in this SOC. The search identified 10 cases of hypersensitivity or anaphylaxis/anaphylactoid reactions, which included 4 serious cases of anaphylactic reactions (2 resolved, 1 improved and 1 with insufficient information regarding the outcome); 4 serious cases of anaphylactoid reaction (all resolved); 1 serious case of drug hypersensitivity (revolved); and 1 serious case of hypersensitivity (resolved). A review of these cases found that all events were reported to have occurred on either the second or third infusion of TCZ.

In 3 cases the patients had some systemic symptoms upon the preceding dose but were administered the subsequent dose at which the event occurred. The age range of patients identified in these cases was 29 months to 17 years of age and all were treated for the indication of juvenile arthritis. The 3 other events identified in *Immune System Disorders*

included 1 serious case of immunodeficiency (unknown outcome), 1 case of polyarteritis nodosum (insufficient information was provided regarding the outcome) and 1 non-serious case of seasonal allergy (resolved). The event of immunodeficiency occurred in a female patient who experienced tiredness, weakness and having a pale appearance after each infusion of TCZ. It was reported that the patient also experienced tongue itching during the infusions but continued to receive TCZ treatment. The patient had been hospitalised for a rotavirus infection. An event of polyarteritis nodosa was reported in the literature. This case concerned a 10 year old male patient treated with TCZ for sJIA in whom polyarteritis nodosa was suspected as a reason for cerebral infarction developing during treatment with TCZ.

Summaries of all fatal cases

The sponsor provided the requested narrative and summaries of the 12 other fatal cases.

A review of the detailed case information found that 11 of the patients identified were treated with TCZ for juvenile arthritis, and 1 was treated for multiple congenital abnormalities. Most patients had a complicated clinical course of events that led up to the fatal outcomes. In 2 cases, both children were born with multiple congenital abnormalities, which may have contributed to the fatal outcome. In 3 cases, infections were the cause of death and in 2 cases infections were present during the clinical course of events leading up to death. Overall, no trends were identified across these reports with regards to age, time on treatment with TCZ, concurrent conditions, concomitant medications, or events leading to death.

Common features of the cases in which causality was assessed as related to tocilizumab

A review of the 11 cases of death or sudden death identified in the 21 April 20011 search of the Roche Safety Database was performed on all cases that were assessed to be related to TCZ. These cases concerned 8 female and 3 male patients. One of the patients was a male treated with TCZ for sJIA (MCN 771896). In this report, the event originally reported "death" was later amended to "sepsis". Of the 10 adult patients, 9 patients were treated with TCZ for RA and one was treated for non-resectable pancreatic carcinoma. The adult patients ranged in age from 45 years to 83 years of age. A review of the individual case details found that all deaths were unobserved by the reporter. Of the limited available information provided, 5 of the patients were reported to have had an illness or event within the month preceding their deaths. These illnesses included reports of flu symptoms; pneumonia; an acute episode of "abnormal breathing" immediately prior to death; non-resectable pancreatic carcinoma involving the portal vein and pancreatic artery; and Epstein-Barr virus infection with liver impairment followed by pneumonia. In 5 cases very limited information was provided. Of these, 1 patient was reported to have died at home 10 hours after the first infusion of TCZ, 1 patient had been in a road traffic accident 2 months prior to his death and in the 3 other cases no details of the patient's deaths were provided. Overall, there were no common trends noted across these reports with regards to age, gender, medical history, concomitant medications or duration of treatment with TCZ. Routine pharmacovigilance of TCZ includes a monthly review of fatal cases received by Roche.

Potential risk of vaccination (lack of effect)

As per the PI, live and live attenuated vaccines should not be given concurrently with TCZ as clinical safety has not been established. In accordance with this guidance, in study WA18221, live or attenuated vaccines were not permitted within 4 weeks of the baseline visit, during study conduct or within 12 weeks following the last administration of study medication. It is recommended that all patients, particularly sJIA patients, if possible, be

brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating TCZ therapy. The interval between live vaccinations and initiation of TCZ therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. The sponsor also recognised the concern of the evaluator regarding the efficacy of vaccination in the context of TCZ treatment in sJIA patients. Therefore, the effect of inactivated vaccine in the sJIA population treated with TCZ who are vaccinated will be studied in the longer term extension, part III of study WA18221. Seasonal influenza titres will be obtained for patients who receive the seasonal influenza vaccine. Pre influenza vaccine titres will be obtained at the visit the patient receives the vaccine. Post influenza vaccine titres will be obtained 4, 8 and 12 weeks after vaccine. The inactivated vaccine data generated in Part III will be submitted within the final Part III CSR. In adult patients, the sponsor is also conducting a randomised, parallel group, open label, multicentre study to evaluate the effects of TCZ on vaccination in subjects with active RA receiving background MTX (study NA25256). The primary objective of this study is to evaluate the humoral immune response 5 weeks after vaccination with 23-valent pneumococcal polysaccharide vaccine (Pneumovax) in patients with active RA treated with TCZ in combination with MTX, compared with the humoral immune response in patients treated with MTX alone defined as proportion of patients who respond to ≥6 of 12 anti-pneumococcal antibody serotypes.

Macrophage activation syndrome/haemophagocytic histiocytosis

The terms of macrophage activation syndrome and histiocytosis haemophagocytic are used interchangeably as they represent the reported term for the event and its associated MedDRA preferred term, respectively. These terms are both used to refer to the same event

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

Despite the pivotal trial providing data over only 12 weeks, efficacy for tocilizumab in children and adolescents with systemic juvenile idiopathic arthritis (sJIA) was demonstrated. Further studies, with limited data, suggested that efficacy was maintained for up to 72 weeks. Efficacy persisted for up to 324 weeks, although by this time the numbers of assessable subjects were very small, and it is possible that unresponsive patients have discontinued the drug.

Safety

Overall, reported adverse events (AEs) were more frequent in subjects treated with tocilizumab. The serious AEs reported were either infective or immunologically mediated. There is dose dependent increase in risk of all types of infection, including both serious infections and infections leading to death. It was not clear the extent to which the risks of AEs, and infections in particular, are increased by concomitant treatment with methotrexate. The reports of a single case of macrophage activation syndrome (MAS) resulting in death, and of three cases of haemophagocytic histiocytosis were of some concern, although MAS is a known complication of the underlying disease.

The ACPM continued to have concerns about the protocol for safe administration of tocilizumab. The committee has commented on this aspect of safety previously. For this indication administration within a hospital setting was considered the main requirement. The committee agreed with the Delegate that the protocol required a 30 minute post-

infusion observation period and preferred the withdrawal of both the injectable promethazine and hydrocortisone from the protocol as shown in the Australian Prescriber anaphylaxis wall chart.

Specific conditions of registration which may be considered include:

- the implementation of the latest version of the Australian-specific RMP,

- the provision of the final study reports of the ongoing studies WA18221 and WA19977,

- that administration of tocilizumab for the paediatric indication of sJIA should take place in a hospital with immediate access to medical personnel, at least until there is adequate demonstration of safety of administration in sufficiently large numbers of children,

- enhanced pharmacovigilance monitoring of all serious adverse events.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of safety and efficacy provided for tocilizumab (Actemra) would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Actemra containing tocilizumab, indicated for:

Systemic Juvenile Idiopathic Arthritis

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

Included among the specific conditions of registration were the following:

1. The implementation of version 2 of the Australian specific Risk Management Plan for Actemra and any future versions of that Risk Management Plan agreed to by the sponsor in consultation with the Office of Product Review of the TGA.
2. The provision of the final study reports of the ongoing studies WA18221 and WA19977 as evaluable data within the context of a Category 1 submission(s) as soon as the reports are available.
3. That administration of tocilizumab for the paediatric indication of sJIA should take place in a hospital with immediate access to medical personnel, at least until there is adequate demonstration of safety of administration in sufficiently large numbers of children. The TGA acknowledges that the sponsor should have the opportunity to revisit this condition of registration in the future based upon accumulated safety data from the paediatric population, such data to be assessed upon its merits in the usual way within the context of a Category 1 submission.
4. Enhanced pharmacovigilance monitoring of all serious adverse events including serious infections, serious anaphylactic reactions, serious anaphylactoid reactions, serious hypersensitivity reactions and deaths in children receiving tocilizumab for sJIA or for any other indication via the supplementation of the current 6 monthly PSUR cycle with additional 3 monthly reports during the intervening periods between PSURs. The additional reports are to be submitted to the Office of Product Review for a period of 24 months from the date of approval of the submission. Any deaths are to be notified to the TGA as soon as possible after the event.

5. That the sponsor should maintain an ongoing review of the emergency response protocol used by health professionals for the administration of tocilizumab by IV infusion to ensure that the protocol is at all times consistent with best medical practice.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

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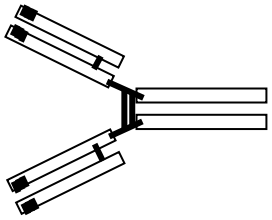
ACTEMRA

Tocilizumab (rch)

CAS 375823-41-9



Tocilizumab 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. Tocilizumab has a molecular weight of approximately 148,000 Daltons. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R).

DESCRIPTION

ACTEMRA is a clear to opalescent, colourless to pale yellow sterile solution for intravenous (IV) infusion. ACTEMRA is supplied in preservative-free, non-pyrogenic single-use, clear glass vials. ACTEMRA is available in 10 mL and 20 mL vials containing 4 mL, 10 mL or 20 mL of tocilizumab concentrate (20 mg/mL). ACTEMRA also contains polysorbate 80, sucrose, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate dihydrate and water for injections.

PHARMACOLOGY

Mechanism of Action

Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Tocilizumab binds specifically 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.

PHARMACODYNAMICS

In clinical studies with tocilizumab, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed. Rapid increases in haemoglobin levels (within the first 2 weeks) were also observed, through

tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts (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 demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see PRECAUTIONS - Haematological Abnormalities).

PHARMACOKINETICS

Rheumatoid Arthritis

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

The following parameters are valid for a dose of 8 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 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. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 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, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see DOSAGE AND ADMINISTRATION).

The following parameters are valid for a dose of 4 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800•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}.

Systemic Juvenile Idiopathic Arthritis
The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with systemic juvenile idiopathic arthritis (sJIA) treated with 8 mg/kg (patients with a body weight ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg), given every 2 weeks. The predicted mean (± SD) AUC_{2weeks}, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 µg•hr/mL, 245 ± 57.2 µg/mL and 57.5 ± 23.3 µg/mL, respectively. The accumulation ratio for C_{min} (week12/week2) was 3.2 ± 1.3. The tocilizumab C_{min} was stabilised after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

Absorption and Bioavailability
Not applicable.

Distribution
Following IV dosing, tocilizumab 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 paediatric patients with sJIA, the central volume of distribution was 0.94 L and the peripheral volume of distribution was 1.60 L resulting in a volume of distribution at steady state of 2.54 L.

Metabolism
Not applicable.

Elimination
The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in RA patients and 7.1 mL/h in paediatric patients with sJIA. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The half life ($t_{1/2}$) of tocilizumab is concentration-dependent in RA, 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. The $t_{1/2}$ of tocilizumab in children with sJIA is up to 23 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

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 population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ³ 50 mL/min) did not impact the pharmacokinetics of ACTEMRA. ACTEMRA has not been studied in patients with moderate to severe renal impairment. (See CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

Other special populations: Population pharmacokinetics in adult rheumatoid arthritis patients showed that age, gender and race did not affect the pharmacokinetics of ACTEMRA. No dose adjustment is necessary for these demographic factors.

CLINICAL TRIALS

Rheumatoid Arthritis

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

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 with a planned interim analysis at week 24 and week 52, 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 percent of patients achieving ACR 20, 50 and 70 responses in Studies I to V are shown in Table 1.

Table 1 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 all studies, 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 on going 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 2).

Table 2 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.

Major Clinical Response
After 2 years of treatment with 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 3).

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

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Table 3 Radiographic mean changes at 52 and 104 weeks in study II (LITHE)

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

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.

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. 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.

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.

Systemic Juvenile Idiopathic Arthritis

The efficacy of ACTEMRA for the treatment of active sJIA was assessed in a 12-week randomised, double blind, placebo-controlled, parallel group, 2-arm study. Patients (treated with or without MTX) were randomised (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 4 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, tocilizumab 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.

INDICATIONS

Rheumatoid Arthritis
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; or
- 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.

Systemic Juvenile Idiopathic Arthritis
ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. ACTEMRA can be given alone or in combination with methotrexate (MTX).

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 PRECAUTIONS)

PRECAUTIONS

All Indications

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including ACTEMRA (see ADVERSE EFFECTS). ACTEMRA treatment should not be initiated in patients with active infections (see 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.

Vigilance for the timely detection of serious infection is recommended for patients receiving biologic treatments for moderate to severe RA or sJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients and parents/guardians of minors with sJIA 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 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.

Complications of Diverticulitis

Events of diverticular perforation as complications of diverticulitis have been reported in RA patients. 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 for RA and sJIA, 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.

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.

It is recommended that all patients, particularly sJIA patients, if possible, 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.

Hypersensitivity Reactions

Serious hypersensitivity reactions have been reported in association with infusion of ACTEMRA in approximately 0.3 % of patients (see ADVERSE EFFECTS – Infusion Reactions). A patient with a previous infusion reaction and premedicated with steroids and antihistamines experienced a fatal anaphylactic reaction during a subsequent treatment with ACTEMRA in the post-marketing setting (see POST-MARKETING EXPERIENCE). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with ACTEMRA. 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 to any component of the product must not be re-challenged with ACTEMRA (see 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.

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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 when considering treatment of patients with active hepatic disease or hepatic impairment (see ADVERSE EFFECTS – Laboratory Abnormalities and DOSAGE AND ADMINISTRATION – Special Patient Groups).

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.

Hepatic Transaminase and Laboratory Effects

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases and bilirubin have been reported with ACTEMRA treatment, without progression to hepatic injury (see ADVERSE 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.

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

ALT and AST levels should be monitored in RA every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see DOSAGE AND 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.

In sJIA ALT and AST should be monitored at the time of the second infusion and thereafter according to good clinical practice (see DOSAGE AND ADMINISTRATION).

Haematological Abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with ACTEMRA 8 mg/kg in combination with MTX (see section ADVERSE EFFECTS – Laboratory Abnormalities). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low neutrophil or platelet count (i.e. ANC < 2 x 10^9/L or platelet count < 100 x 10^9/L). In patients with an ANC < 0.5 x 10^9/L or a platelet count < 50 x 10^9/L treatment is not recommended (See PRECAUTIONS – Effects of Laboratory Tests).

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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.

Neutrophils and platelets should be monitored in RA 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 DOSAGE AND ADMINISTRATION.

In sJIA neutrophils and platelets should be monitored at the time of the second infusion and thereafter according to good clinical practice (see DOSAGE AND ADMINISTRATION).

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 ADVERSE EFFECTS – Elevations in lipid parameters). 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 RA and sJIA 4 to 8 weeks following initiation of ACTEMRA therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

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.

Malignancy

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

Infusion Reactions

Infusion reactions have been observed during and within 24 hours of treatment with ACTEMRA (see ADVERSE EFFECTS – Infusion Reactions).

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 PRECAUTIONS – 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

This medicinal product 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'.

Effects on Fertility

Preclinical data do not suggest an effect on fertility under treatment with a murine analogue of tocilizumab. Effects on endocrine active organs or on organs of the reproductive system were not seen in a chronic cynomolgus monkey toxicity study, nor was 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 tocilizumab and anti-tocilizumab 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 tocilizumab into the milk of lactating mice has been observed.

Use in Children

The safety and efficacy of ACTEMRA in children below 18 years of age with conditions other than sJIA have not been established. Children under the age of two have not been studied.

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.

Use in the Elderly

Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of ACTEMRA in adult rheumatoid arthritis 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.

Carcinogenicity

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

Genotoxicity

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

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 1×10^9/L occurred in 3.4%, with counts $< 0.5 \times 10^9$/L occurring in 0.3%, of patients on ACTEMRA 8 mg/kg + DMARD without clear association with serious infection (see PRECAUTIONS – Haematological Abnormalities; ADVERSE EFFECTS - Laboratory Abnormalities). In patients with an absolute neutrophil count $< 0.5 \times 10^9$/L treatment is not recommended.

Ability to Drive and Use Machines

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

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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 ADVERSE EFFECTS).

INTERACTIONS WITH OTHER MEDICINES

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance.

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

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 tocilizumab, 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. Tocilizumab 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 tocilizumab, 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 ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

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ADVERSE EFFECTS

Rheumatoid Arthritis

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 4 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 rheumatoid arthritis 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 lymphaticsystem 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 pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have also been reported.

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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.

In the 6 month controlled clinical trials, the rate of anaphylactic reactions in those receiving the lower dose of 4 mg/kg was 3/744 (0.4%) and in the higher dose of 8 mg/kg was 3/1870 (0.2%). As anaphylactic reactions tend to occur early in the course of treatment, the overall rate of anaphylaxis cumulatively in the long term extensions remained at 6/3778 or 0.2%.

Clinically significant hypersensitivity reactions associated with ACTEMRA and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) 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-tocilizumab antibodies in the 6 month controlled clinical trials. Forty six patients (1.6%) developed positive anti-tocilizumab antibodies of whom 5 had an associated medically significant hypersensitivity reaction leading to withdrawal. Thirty patients (1.1%) developed neutralising antibodies.

Systemic Juvenile Idiopathic Arthritis

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

In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see ADVERSE EFFECTS – Rheumatoid Arthritis).

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Infections

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

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, 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 ACTEMRA. One patient in the placebo group escaped to 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. In the 12 week controlled trial, 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 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 ACTEMRA and requiring treatment discontinuation were reported in 1 out of 112 patients (<1%) treated with ACTEMRA during the controlled and open-label parts of the clinical trial.

Reports of anaphylaxis, anaphylactoid reactions, and hypersensitivity reactions in patients under 18 years of age have been reported in the post-marketing setting.

Immunogenicity

All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal.

Laboratory Abnormalities

Haematology abnormalities

Rheumatoid Arthritis

Neutrophils

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 (see PRECAUTIONS – Effects on Laboratory Tests).

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

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

Platelets

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 DOSAGE AND ADMINISTRATION and PRECAUTIONS – Haematological Abnormalities.)

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.

Systemic juvenile idiopathic arthritis
During routine laboratory monitoring in the 12 week controlled trial, a decrease in neutrophil counts below 1×10^9/L occurred in 7% of patients in the ACTEMRA group, and in none in the placebo group. In the ongoing open-label extension study decreases in neutrophil counts below 1×10^9/L occurred in 15% of patients in the ACTEMRA group.

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

During routine laboratory monitoring in the 12 week controlled trial, 3% of patients in the placebo group and 1% in the ACTEMRA group had a decrease in platelet count to $\leq 100 \times 10^3/\mu L$. In the ongoing open-label extension study decreases in platelet counts below $100 \times 10^3/\mu L$ occurred in 3% of patients in the ACTEMRA group, without associated bleeding events.

Liver enzyme elevations

Rheumatoid Arthritis
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. These elevations were not associated with any clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency. During routine laboratory monitoring, the incidence of indirect bilirubin > 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.

Systemic juvenile idiopathic arthritis
During routine laboratory monitoring in the 12 week controlled trial, elevation in ALT or AST $\geq$ 3 x ULN occurred in 5% and 3% of patients, respectively, in the ACTEMRA group, and in 0% of placebo patients.

In the ongoing open-label extension study, elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients, respectively, in the tocilizumab group.

Elevations in lipid parameters

Rheumatoid Arthritis

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.

Systemic juvenile idiopathic arthritis

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

In the ongoing open-label extension study the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled trial data.

Malignancies

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

Post-Marketing Experience

The safety profile in post-marketing experience is consistent with clinical trial data with the exception of a case of fatal anaphylactic reaction which has been reported during post-marketing experience (see PRECAUTIONS – Hypersensitivity Reactions).

Globally, serious hypersensitivity reactions related to ACTEMRA exposure reportedly occur at a rate of approximately 0.26%. In Australia this rate is approximately 0.17%. The one fatal anaphylactic reaction, which has been reported, occurred when the patient was re-challenged with ACTEMRA despite previously experiencing a hypersensitivity reaction to ACTEMRA (see CONTRAINDICATIONS).

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DOSAGE AND ADMINISTRATION

Treatment should be initiated by healthcare professionals experienced not only in the diagnosis and treatment of RA or sJIA but also in the use of biological therapies for this condition.

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.

Rheumatoid Arthritis in Adults

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 PHARMACOLOGY – PHARMACOKINETICS).

The calculated dose of ACTEMRA should be diluted to 100 mL and administered as an IV infusion over a period of 1 hour.

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

Dose Modification Recommendations

- Liver enzyme abnormalities

Lab Value	Action
> 1 to 3 x ULN	Dose modify concomitant DMARDs if appropriate For 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
> 3 to 5 x ULN (confirmed by repeat testing, see PRECAUTIONS - Hepatic Transaminase	Interrupt ACTEMRA dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN, discontinue ACTEMRA

Elevations)	
> 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 at 4 mg/kg and increase to 8 mg/kg 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 at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue ACTEMRA

Systemic juvenile idiopathic arthritis (sJIA)
The recommended dose of ACTEMRA for patients with sJIA is:

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

given once every two weeks as an IV infusion. A change in dose should only be based on a consistent change in the patient's body weight over time. ACTEMRA can be used alone or in combination with MTX.

ACTEMRA should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (see section Preparing the Infusion).

ACTEMRA is recommended for IV infusion over 1 hour.

Dose Modification Recommendations:
Dose reduction of ACTEMRA has not been studied in the sJIA population. Dose interruptions of ACTEMRA for laboratory abnormalities are recommended in patients with sJIA and are similar to what is outlined above for patients with RA (see

PRECAUTIONS - Haematological Abnormalities). 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 sJIA the decision to discontinue ACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Special Patient Groups

Children: The safety and efficacy of ACTEMRA in children below 18 years of age with conditions other than sJIA have not been established. Children under the age of two have not been studied.

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

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

Hepatic impairment: The safety and efficacy of ACTEMRA has not been studied in patients with hepatic impairment (see PRECAUTIONS – Active Hepatic Disease and Hepatic Impairment) and therefore no dose recommendations can be made.

Preparing the 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.

Rheumatoid Arthritis

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.

sJIA patients ≥ 30 kg

From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the 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.

sJIA Patients < 30 kg
From a 50 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.6 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of ACTEMRA under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

OVERDOSAGE

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

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE

ACTEMRA is available as:
*(not marketed)

- 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.

Store vials at 2ºC – 8ºC. (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 – 8ºC for not more than 24 hours.

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Do not use after the expiry date (EXP) shown on the pack.

Disposal of Medicines
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.

POISON SCHEDULE

Prescription Only Medicine (S4)

SPONSOR

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Dee Why NSW 2099
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Distributed in New Zealand by:
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NEW ZEALAND

Customer enquiries: 0800 656 464

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

21 May 2009

DATE OF MOST RECENT AMENDMENT

31 October 2011

Therapeutic Goods Administration

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