Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tocilizumab

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

February 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The 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 <http://www.tga.gov.au>.

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 indication
Decision:	Approved
Date of Decision:	4 October 2013
Active ingredient:	Tocilizumab (rch)
Product Name:	Actemra
Sponsor's Name and Address:	Roche Products Pty Ltd 4-10 Inman Road Dee Why NSW 2099
Dose form:	Injection concentrated
Strength:	20 mg/mL
Container:	Vial
Pack sizes:	1 vial, 4 vials
New Approved Therapeutic use:	Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate (MTX). Actemra can be given alone or in combination with methotrexate (MTX).
Route of administration:	Intravenous
Dosage:	The recommended dose of Actemra for patients with pJIA is 10 mg/kg for patients <30 kgs, and 8 mg/kg for patients ≥30 kgs, given once every four weeks as an intravenous infusion.
ARTG Numbers:	149402, 149403, 149404

Product background

Tocilizumab (TCZ) is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 (gamma 1) subclass, directed against the interleukin 6 (IL-6) receptor. It is composed of two heterodimers, each of which is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bridges.

TCZ binds specifically to both soluble and membrane-bound IL-6 (sIL-6R- and mIL-6R-) receptors and has been shown to inhibit sIL-6R- and mIL-6R-mediated signalling. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including rheumatoid

arthritis (RA). In clinical studies with TCZ, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed.

Actemra was first approved in Australia in May 2009 for the treatment of moderate to severe active RA in adult patients. In October 2010 the indication was extended to include inhibition of the progression of joint damage, as measured by X-ray, when given in combination with methotrexate (MTX). In October 2011 the indication was further extended to include systemic juvenile idiopathic polyarthritis (sJIA) in patients 2 years of age and older.

The current indications are:

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 MTX.*

Systemic Juvenile Idiopathic Arthritis:

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

This AusPAR describes the application by Roche Products Australasia Pty Ltd (the sponsor) to extend the indications for Actemra to the following proposed new indication:

Polyarticular Juvenile Idiopathic Arthritis:

Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to MTX. Actemra can be given alone or in combination with MTX.

Regulatory status

The product received initial ARTG Registration on 21 May 2009.

Similar applications have been submitted in other countries.

Table 1: International regulatory status

Country	Tradename	Approved	Indications
USA	Actemra	April 2013	Treatment of active pJIA in patients 2 years of age and older.
EU	RoActemra	May 2013	In combination with MTX is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
Japan		April 2008	Treatment of active pJIA
New Zealand		June 2013	Treatment of active pJIA
Canada		Under submission	Treatment of active pJIA
Switzerland		Under submission	Treatment of active pJIA

The information provided is current at the time this application was considered.

Product Information

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

II. Quality findings

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

III. Nonclinical findings

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

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Scope of the clinical dossier

The submission contained the following clinical information:

- Three clinical pharmacology sub-studies, which provided pharmacokinetic (PK) and pharmacodynamic (PD) data collected from 188 subjects with pJIA treated with TCZ in the Cherish Study (also known as Study WA19977), as well as 19 Japanese subjects treated with TCZ in Studies MRA318JP and MRA319JP.
- Two independent population PK (PopPK) analyses of the data obtained in the Cherish Study and Study MRA318JP.
- One pivotal efficacy/safety Study - the Cherish Study.
- No specific dose-finding studies.
- One supporting open-label trial of 12 weeks duration (MRA318JP) providing efficacy/safety data, which had a long-term extension phase (Study MRA319JP).
- One observational cohort study of six months duration in Japanese patients, ML21939, also known as Japanese Post-Marketing Surveillance (JPMS) which provided supporting safety data.

Paediatric data

The submission included paediatric pharmacology, efficacy and safety data as the requested extension of indication is for patients aged 2 years or older.

Good clinical practice

The two main studies (Cherish, and Studies MRA318JP/MRA319JP) evaluating the use of TCZ in children and adolescents with active pJIA were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

PK data for this submission was provided by the single pivotal Cherish Study in which 188 subjects with severely active pJIA were treated with TCZ, with additional PK data provided by the supportive Studies MRA318JP and MRA319JP involving 19 Japanese subjects. The submission also contained two independent PopPK analyses including data obtained from the Cherish Study and Study MRA318JP.

Evaluator's overall conclusions on pharmacokinetics

In this submission, the PK properties of TCZ when used in patients aged 2-19 years with active pJIA was assessed from data collected in a single pivotal Cherish Study, involving 188 patients who received intravenous (IV) TCZ (8 or 10 mg/kg) every four weeks for up to 40 weeks, as well as 19 Japanese subjects involved in the MRA318JP/319JP Studies who were given IV TCZ 8 mg/kg every 4 weeks for up to 168 weeks. The majority of patients

involved in the Cherish Study were female (78%), with Caucasian ethnicity (79%) and had a median age of 11 years. The 19 Japanese subjects in the MRA318JP/319JP Studies were also predominately female (79%; 15/19) with a median age of 12 years.

The key PK findings of the TCZ clinical trial program in patients with active pJIA were:

- TCZ demonstrates moderate between patient variability for clearance (CL), peripheral volume of distribution (Vd) and the maximum elimination rate;
- Differences in subject body surface area (BSA) principally explains the variability in drug CL;
- The Cherish Study (Parts I and II) showed that the model computed (for example, area under the curve (AUC) and maximum concentration (C_{max}), as well as observed PK parameters (that is, C_{trough}) for the TCZ 10 mg/kg dose in subjects with a body weight (BW) <30 kg was most comparable to the drug exposure demonstrated in the patients weighing >30 kg who received TCZ 8 mg/kg;
- Part I (first 16 weeks) of the Cherish Study showed that clinical non-response was associated with a lower exposure to TCZ (as evidenced by AUC and C_{max} results), however, clinical response in Part I of the Cherish Study was not associated with a higher drug exposure;
- Patients with the lowest quartile of drug exposure to TCZ in Part II of the Cherish Study had the lowest incidence of overall adverse events (AEs), and also the two most common types of AEs (infections and gastrointestinal (GI) disorders);
- Study MRA318JP shows that the mean elimination half-life of TCZ at steady state for patients with active pJIA is approximately 123-130 hours;
- Modelled data from Study MRA318JP suggests that if patients weighing <30 kg receive TCZ 8 mg/kg they have a lower drug exposure compared to subjects >30 kg who receive TCZ 8 mg/kg, and that this finding may be associated with a lower rate of clinical response;
- Comparison of the PK data between subjects with pJIA, sJIA and adult RA indicates that patients with BW <30 kg suffering from active pJIA require a dose of TCZ 10 mg/kg (versus 8 mg/kg) every four weeks to achieve a comparable drug exposure to the other TCZ arthritis treatment indications.

Pharmacodynamics

Studies providing pharmacodynamic data

Pharmacodynamic (PD) data for this submission was provided by the single pivotal Cherish Study with 188 subjects with severely active pJIA treated with TCZ, with additional PD data provided by the supportive Studies MRA318JP and MRA319JP involving 19 Japanese subjects.

Evaluator's overall conclusions on pharmacodynamics

In this submission, the PD properties of TCZ when used in patients aged 2-19 years with active pJIA was assessed from data collected in the Cherish Study involving 188 patients who received IV TCZ (8 or 10 mg/kg) every four weeks for up to 40 weeks, as well as 19 Japanese subjects involved in the MRA318JP/319JP studies who were given IV TCZ 8 mg/kg every four weeks for up to 168 weeks. The majority of patients involved in the Cherish Study were female (78%), with Caucasian ethnicity (79%) and had a median age

of 11 years. The 19 Japanese subjects in the MRA318JP/319JP Studies were also predominately female (79%; 15/19) with a median age of 12 years.

The sponsor has appropriately nominated mean changes in serum IL-6R and sIL-6 R levels as the primary PD markers of interest for TCZ. Mean serum changes in serum inflammatory markers (ESR and CRP) were evaluated as the secondary PD biomarkers of relevance.

Expectedly for the mechanism of action of TCZ, the pivotal and supporting studies demonstrated a decrease in serum inflammatory markers (CRP and ESR) within two to four weeks of first administration. Similarly, the mean values for sIL-6R increased rapidly (one to four weeks) following TCZ infusion and remained constant thereafter for extended periods of follow-up (at least 40 weeks). In the Cherish Study, the small subgroup of patients with a BW <30 kg who received TCZ 8 mg/kg (n=11), recorded mean sIL-6R concentrations from Weeks 12 to 40 that were approximately half the value of the other two TCZ dose groups. This suggests that the higher dose of TCZ (10 mg/kg) may be required in patients with BW <30 kg to achieve the optimal PD response equating to dosing with TCZ 8 mg/kg in patients with BW >30 kg. Mean serum IL-6 concentrations increased rapidly in the first week following TCZ infusion in the Cherish Study, and then declined to its baseline value by Week 4, then fluctuated up to three-fold above baseline between administered doses, but in general remaining low between Weeks 4 and 16. No consistent difference in the mean value for serum IL-6 was seen in any of the three TCZ treatment groups. Mean serum IL-6 concentrations did not show any significant change over time in the supporting Studies MRA318JP and MRA319JP.

The MRA318JP and 319JP Studies showed that CRP (<1.0 mg/dL) and ESR (<18 mm/hr) were within the normal range when serum TCZ concentrations were maintained above 1.0 μg/mL (the Lower Limit of Quantification (LLQ)) throughout the TCZ dosing cycle. Furthermore, serum sIL-6R concentrations reached a plateau when the serum TCZ concentration was around a level of 10 μg/mL.

Dosage selection for the pivotal studies

Although no specific dose-finding studies have been performed for patients with active pJIA, the dose and administration frequency of TCZ used in the pivotal Cherish Study, and proposed by the sponsor for licensing, has been reasonably justified by the sponsor. The sponsor is proposing that TCZ be administered every four weeks by IV infusion at a dose of 8 mg/kg for those with a BW of ≥30 kg, and a dose of 10 mg/kg in children with a BW of <30 kg. In the pivotal trial patients weighing <30 kg were randomised 1:1 to either TCZ 8 or 10 mg/kg. The rationale for assessing the higher TCZ dose in children of lower BW is based on PK/PD modelling data obtained in Study MRA318JP. The simulation results suggest that TCZ 10 mg/kg every four weeks (q4w) in patients with BW <30 kg should be able to achieve a comparable drug exposure to that observed in patients weighing ≥30 kg who are administered TCZ 8 mg/kg.

The approved TCZ dose in patients with sJIA is dependent on the patient's BW, using two weight bands with a cut-off value of 30 kg. In sJIA, TCZ is administered more frequently (every two weeks) and also at a higher dose (12 mg/kg for those with BW <30 kg; and 8 mg/kg for subjects weighing ≥30 kg). The adjustment of TCZ dosing using weight bands in sJIA has resulted in comparable PK exposure and efficacy outcomes across the range of BW. Children with sJIA have a higher clearance of TCZ (mean of 7.1 mL/hr) compared to those with pJIA (mean CL=5.8 mL/hr) which justifies the shorter dosing interval.

The doses of background treatment with MTX, corticosteroids (CS) and non-steroidal anti-inflammatory drugs (NSAIDs) when used by patients in the pivotal Cherish study were appropriate, and consistent with contemporary clinical practice in Australia.

Efficacy

Studies providing efficacy data

Two studies were provided.

The Cherish Study (also known as Study WA19977)

The Cherish Study is a Phase III, randomised, active treatment then withdrawal trial conducted in three parts to evaluate the efficacy of TCZ in patients with pJIA

The main objective of the study was to evaluate the efficacy and safety of TCZ in patients with active pJIA with a history of an inadequate response to MTX (due to either lack of efficacy or toxicity), who were receiving the standard of care with or without NSAIDs, low dose CS, or concomitant MTX. The primary efficacy outcome was to compare the proportion of patients on TCZ versus placebo who developed a JIA American College of Rheumatology (ACR) 30[1] flare by Week 40 compared to Week 16. Secondary objectives included assessment of the efficacy of continued, open-label TCZ in terms of maintenance of clinical response (not presented in this submission), as well as the efficacy and safety of TCZ 8 mg/kg versus 10 mg/kg in patients weighing < 30 kg.

Studies MRA318JP and MRA319JP

Study MRA318JP was an open-label, single arm, Phase III study conducted in five centres in Japan between November 2004 and July 2005. The primary objective of the study was to evaluate the short-term safety, efficacy and PK of TCZ in patients with pJIA.

Evaluator's conclusions on clinical efficacy

JIA affects approximately one in 1000 children in Australia, and 30% of cases are polyarticular. There is significant unmet need for additional effective therapies as response to current treatment options is variable. In support of the extension of indication of TCZ to include the treatment of active pJIA in patients 2 years of age and older, the sponsor has provided data from a single pivotal Phase III study (the Cherish Study) which had a 16-week, open-label, active treatment, lead-in period; followed by a randomised withdrawal phase in treatment responders (Weeks 16-40). The study recruited 188 patients who had demonstrated either an inadequate response to or intolerance of MTX, and prior biologic use was recorded in 32% of the study participants. Supportive evidence of efficacy was provided by a 12-week, open-label, single-arm Phase III Study (MRA318JP) which enrolled 19 Japanese subjects. This study had a long-term extension phase (MRA319JP) whereby the 19 patients received ongoing TCZ for up to 168 weeks. The submission is consistent with the TGA adopted specific regulatory guideline pertaining to the requested extension of indication: European Union (EU) guideline CPMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis" (effective 26 June 2009). In particular, the trial design of the pivotal study was appropriate for the claimed indication and studied a sufficient number of patients for an acceptable duration of therapy. For the Cherish Study, randomisation procedures, strategies to maintain blinding, choice of efficacy endpoints and statistical analysis were appropriately performed.

The Cherish Study enrolled patients with severely active pJIA, and demonstrated that TCZ is an effective treatment in those who have either failed or are intolerant to MTX. The primary efficacy endpoint of the Cherish Study was met, whereby a statistically significant difference in the rate of JIA ACR30 flares at Week 40 (compared with Week 16) was detected between the control group (48.1%; 39/81) and TCZ treated patients was

[1] Represents a 30% improvement from baseline in at least three of six response criteria without a worsening of greater than 30% in one remaining response variable and the absence of a fever.

observed (25.6%; 21/82). This result also represents a clinically meaningful, treatment related outcome. The secondary efficacy endpoint analysis also showed that while 89.4% of TCZ treated patients had a JIA ACR30 response at Week 40, the majority of patients achieved an even higher level of clinical response (JIA ACR50 83%, JIA ACR70 62% and JIA ACR90 26%). The timeline to achieve these responses was relatively rapid with the majority of the clinical effect evident in the first 12 weeks of treatment. Response to TCZ treatment was also seen using different outcome measures such as Juvenile Arthritis Disease Activity Score (JADAS)-27 and pain Visual Analogue Scale (VAS) scores. A proportion of patients (31.7%) achieved inactive disease status at Week 40.

The majority (79%) of patients in the pivotal study population were taking MTX during the study treatment period. A lower rate of JIA ACR30 flares at Week 40 was observed in patients receiving MTX concurrently with TCZ. In contrast, there was no consistent difference in the JIA ACR30 flare rate in patients receiving a stable dose of CS (limited to 0.2 mg/kg/day, or a maximum of prednisone 10 mg/day) during the study period. Approximately, one third of subjects in the Cherish Study population had received at least one biologic disease modifying anti-rheumatic drug (DMARD) prior to entry. The biologic DMARD experienced patients had a higher rate of JIA ACR30 flare at Week 40, and lower rates of JIA ACR30/50/70/90 responses in both the TCZ and placebo groups, compared to patients not previously exposed to biologic DMARD. This is to be expected and reflects a relatively treatment refractory subgroup of patients. Rheumatoid factor status had no influence upon the clinical efficacy response to TCZ.

The baseline demographic and disease related characteristics of patients in the pJIA TCZ treatment studies are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. The majority of patients were female (77%), of Caucasian ethnicity (80%) with a mean age of 11 years. However, there are some caveats to making generalisations concerning the treatment population. The Cherish Study excluded patients who were at a significant risk of infection, or who had various abnormal laboratory results at baseline (for example, abnormal haematology or liver function tests).

The Cherish Study found a small difference in the rate of JIA ACR30 response in patients with BW <30 kg according to dose of TCZ administered. In this subgroup, a higher rate of JIA ACR30 response was seen with the 10 mg/kg dose of TCZ compared with 8 mg/kg. This difference was also seen across the other JIA ACR response categories. This is consistent with the increased efficacy seen in patients with sJIA who have a BW <30 kg treated with a higher dose of TCZ. However, statistical significance could not be demonstrated in the Cherish Study due to the low subject numbers.

The MRA318JP and MRA319JP Studies are supportive of the key efficacy findings of the pivotal trial by demonstrating:

- JIA ACR30 response was seen in 94.7% (18/19) of patients after 12 weeks of TCZ treatment in Study MRA318JP, the rate of JIA ACR30 response was 94.1% (16/17 of patients) at 24 weeks, and 100% for each 24 week period between Weeks 48 and 168 (excluding patient withdrawals at each time point) indicating sustained response in many individuals.
- High rates of JIA ACR50 response rate (94.7%) and JIA ACR70 response (57.9%) in Study MRA318JP were maintained during the long-term, OLE phase.
- All six of the JIA ACR core set variables showed a rapid and sustained improvement from baseline in Study MRA318JP, which continued to Week 168 in the OLE Study MRA319JP.

- A possible CS sparing effect with the proportion of patients whose dose of CS had decreased by at least 50% from baseline was 7.1% (1/14) at 24 weeks, 28.6% (4/14) at 48 weeks, 84.6% (11/13) at 108 weeks and 84.6% (11/13) at 156 weeks.

Overall the efficacy data in this submission supports the efficacy of TCZ in the treatment of moderately-severely active pJIA (as per the International League of Associations for Rheumatology (ILAR) criteria), with or without MTX, in patients aged 2 years to 18 years. For maximum clinical benefit, concurrent MTX treatment is preferred in patients who are not intolerant to MTX. In MTX intolerant patients, TCZ monotherapy has demonstrated sufficient efficacy in treating severely active pJIA. Patients weighing <30 kg should receive TCZ every four weeks at a dose of 10 mg/kg, and all other patients should receive TCZ 8 mg/kg every four weeks.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

There was a single pivotal efficacy study (Cherish), which collected the following safety data:

- General AEs were assessed by AE reporting and clinical assessment performed at weekly intervals during Part I and II of the study (first 40 weeks).
- AEs of special interest, including infections, infusion reactions, neutropenia, thrombocytopenia, abnormal liver function tests, and GI AEs, were assessed by their overall rate and number of individual events.
- Laboratory tests, including haematology, chemistry and urinalysis performed at baseline, weekly for the first four weeks of the trial; and then every one to four weeks for the remainder of the first 40 weeks of treatment follow-up.
- Anti-TCZ antibodies were assessed at baseline, Weeks 20, 27, 34 and 40, or during any flare visit in Part II of the study.
- Chest imaging (by plain x-ray) was performed at baseline and Week 20.

AE reporting was standardised by the sponsor for analysis by assigning preferred terms as set out in the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1. All AEs were graded according to the National Cancer Institute's Common Terminology Criteria (Version 3.0).

Pivotal studies that assessed safety as a primary outcome

There were no studies that assessed safety as the primary outcome.

Dose-response and non-pivotal efficacy studies

No specific dose-response studies have been conducted but additional safety data was provided by the following non-pivotal efficacy studies:

- Study MRA318JP which was a 12-week, open-label TCZ treatment trial involving 19 Japanese children with active pJIA, and
- Study MRA319JP which was the long-term OLE phase of Study MRA318JP involving 19 Japanese children who were followed for up to 168 weeks.

Other studies evaluable for safety only

Supporting safety data collected as part of the regulatory requirement for the Japanese Post-Marketing program (Study ML21939) was also presented in this submission.

Summary of patient/drug exposure

A total of 188 patients received TCZ in the Cherish Study and all of these subjects were included in the safety analysis. Of the 188 patients, 28 received TCZ 10 mg/kg, 153 received TCZ 8 mg/kg (119 patients weighed at least 30 kg, and 34 patients had BW <30 kg), and seven switched from TCZ 10 to 8 mg/kg. All seven of the TCZ dose switches were due to the subjects increasing their BW by at least 5 kg (and above 30 kg) during the study. As the Cherish Study was on-going at the time of this submission (data cut-off date of 4 November 2011), the median exposure to TCZ was 0.92 years which represents a total of 184.4 patient-years (PY) of exposure. A summary of exposure to TCZ in the Cherish Study is presented in Table 2. Most (94%) of patients received all four TCZ infusions in Part I of the trial. During Part II, a greater percentage of subjects received all six infusions of TCZ (70%; 57/82) compared to those administered placebo IV infusions (53%; 43/81).

Table 2: Summary of Exposure to TCZ and Duration of Follow-Up in Study WA19977

	TCZ 10 MG/KG (<30KG) N = 28	TCZ 10 MG/KG to TCZ 8 MG/KG (<30KG) N = 7	TCZ 8 MG/KG (<30KG) N = 34	TCZ 8 MG/KG (>=30KG) N = 119	ALL TCZ N = 188
Exposure to TCZ (Weeks)					
Mean	48.40	64.82	37.76	52.73	49.09
SD	24.691	15.098	24.961	25.009	25.424
SEM	4.665	5.707	4.281	2.295	1.854
Median	49.36	67.29	40.14	51.43	48.14
Min-Max	12.1 - 89.3	40.4 - 84.3	0.1 - 92.1	0.1 - 96.1	0.1 - 96.1
Sum	1215.1	453.7	1283.9	6275.4	9228.1
n	28	7	34	119	188
Exposure to TCZ (Years)					
Mean	0.69	1.24	0.72	1.01	0.94
SD	0.472	0.289	0.476	0.480	0.487
SEM	0.089	0.109	0.082	0.044	0.036
Median	0.83	1.29	0.77	0.99	0.92
Min-Max	0.2 - 1.7	0.8 - 1.6	0.0 - 1.8	0.0 - 1.8	0.0 - 1.8
Sum	23.3	8.7	24.6	120.9	176.9
n	28	7	34	119	188
Duration in Study (Weeks)					
Mean	46.00	64.82	41.63	54.34	51.19
SD	22.148	15.098	21.725	23.632	23.404
SEM	4.186	5.707	3.726	2.166	1.707
Median	44.36	67.29	42.21	53.00	48.29
Min-Max	16.0 - 89.3	40.4 - 84.3	10.1 - 92.1	4.1 - 97.4	4.1 - 97.4
Sum	1288.0	453.7	1415.3	6466.9	9623.9
n	28	7	34	119	188

The exposure to TCZ in Studies MRA318JP and 319JP was summed from the first infusion in MRA318JP until the last observation recorded in the OLE trial (MRA319JP). A total of 19 patients were included in this safety population with median treatment duration of 3.22 years (range: 0.35-3.53 years). The total exposure to TCZ was 55.7 PY. The mean dose of TCZ administered was 8.56 mg/kg every four weeks.

Deaths and other serious adverse events

Pivotal study

No deaths have been reported in the all exposure population of the Cherish Study.

However, 17 patients (9.0% of 188) have reported 22 serious adverse events (SAEs) at a rate of 12.5 SAEs per 100 PY. Given the overall low number of SAEs, no meaningful difference between the patient weight and TCZ dosage groups can be concluded. The two most common SAE categories (by System Organ Class (SOC)) were infection (nine patients; 4.8% of 188; 4.9 per 100 PY) and injury/poisoning/procedural complications (three patients; 1.6%; none of which were treatment related). The infection related SAEs included four patients with pneumonia (three of whom were >30 kg and received TCZ 8 mg/kg; and one had BW <30 kg and was given TCZ 10 mg/kg), two subjects reporting bronchitis (both had BW <30 kg and received TCZ 10 mg/kg) and two patients developing cellulitis (both weighed > 30 kg and received TCZ 8 mg/kg). Another patient with BW <30

kg who received TCZ 8 mg/kg developed varicella pneumonitis. Other noteworthy individual types of SAEs included benign intracranial hypertension (14 year old female weighing 85 kg; onset Day 6) and uveitis (patient <30 kg on TCZ 8 mg/kg; indicating treatment failure).

Other studies

No deaths were recorded in the MRA318JP and MRA319JP Studies. However, four patients reported six SAEs. These events included two cases of gastroenteritis; and singular reports of influenza, pneumonia, myasthenia gravis and sensory disturbance. The patient who developed myasthenia gravis was withdrawn from the study on Day 615, and treated appropriately (IV CS, plasmapheresis and tacrolimus). The SAE was considered to be possibly related to TCZ.

Evaluator's overall conclusions on clinical safety

The total clinical safety dataset for the use of TCZ in patients aged 2-19 years with active pJIA consists of a patient exposure of 386 patients in four studies, all of whom received TCZ 8-10 mg/kg every four weeks by IV infusion. Most of the patients received concurrent MTX and low dose oral CS.

In the pivotal Cherish Study, 177/188 (94%) of patients received all four scheduled infusions of TCZ during Part I. During Part II of the trial, 57/82 (69.5%) received all six planned infusions of TCZ and 43/81 (53.1%) of subjects were given all six scheduled placebo infusions. At the time of data cut-off (4 November 2011), the median exposure to TCZ in the Cherish Study was 48 weeks and the total duration of TCZ exposure was 184.4 PY. In the supporting Studies MRA318JP and MRA319JP, open-label TCZ treatment was given to 19 Japanese subjects for 0.35-3.5 years, representing a TCZ exposure of 55.7 PY. In addition, the submission contained safety data from a post-marketing experience in 179 Japanese subjects treated with TCZ for pJIA who were followed a median duration of six months. The total duration of TCZ exposure in this cohort (known as JPMS) was 93.63 PY. There is sufficient data to make a meaningful assessment of safety in the short to medium-term (almost up to one year), however long term (multi-year) safety data is not yet available in the paediatric population.

Infection was the most common AE recognised in the TCZ pJIA studies with 61.2% of patients in the pivotal study experiencing an infection related AE. The majority of infections were mild in severity, self-limiting and predominately involved either the upper respiratory tract or GI system. However, nine infectious SAEs at a rate of 4.9 per 100 PY in the Cherish Study were reported, with the most common site being the respiratory tract. One patient in the pivotal study developed pulmonary tuberculosis. The use of concurrent MTX and/or CS does not appear to increase the risk of infection associated with TCZ use. Subject weight and TCZ dose (8 or 10 mg/kg in those weighing <30 kg) did not appear to be a determinant of infection. However, a greater proportion of AEs resulting in TCZ dose interruptions were observed in patients with BW <30 kg who received 10 mg/kg (28.6%; 8/28) versus 8 mg/kg (5.9%; 2/34), and the most common reason for TCZ dose interruption was intercurrent infection.

Infusion related AEs (either during or within 24 hours of administration) occurred in patients given TCZ. In the Cherish Study, 11 subjects (5.6% of 188) experienced an AE during and 33 patients (17.6% of 188) reported an AE within 24 hours of having an infusion. A higher rate of infusion related reactions were seen in the subjects weighing >30 kg in the Cherish Study compared to those with BW <30 kg (regardless of TCZ dose). In the supporting MRA studies, two patients were observed to have experienced infusion related reactions. The majority of infusion related AEs (during or within 24 hours of administration) were mild and resolved without specific intervention.

No deaths were reported in the pivotal or supporting studies. However three deaths were identified in the post-marketing surveillance, of which infection was contributory in at least two of these cases.

Some patients developed significant abnormalities in haematological parameters during the studies involving patients with pJIA. Nearly one third of patients (31.4%) experienced a decline in neutrophil count from baseline in the Cherish Study, and seven patients developed Grade 3-4 neutropenia in this trial. Thrombocytopenia was identified in 15 patients (8.0% of 188) during the Cherish Study. None of the haematological changes were associated with infection or bleeding, or required withdrawal from TCZ.

Elevations in hepatic transaminases (AST and ALT) were occasionally seen in patients treated with TCZ. The majority of these changes in liver function tests were mild and transient. Minor elevations of serum total bilirubin were also seen in up to 14.5% of patients in the Cherish Study, but without associated clinical implications. Adverse changes in lipid profile (mainly, increases in total serum cholesterol) were observed during TCZ treatment in 34.6% of patients in the Cherish Study. Minor elevations in triglyceride levels were also seen. The long-term clinical significance of these lipid changes in children is unknown, however monitoring of serum lipids should be considered.

The incidence of developing anti-TCZ antibodies is low (2.1%-5.3%) and their clinical relevance is yet to be defined with no discernible link to the risk of infection, infusion related reactions or loss of efficacy.

In summary, the safety data indicates that TCZ has an acceptable overall safety profile in the treatment of pJIA in patients aged 2 to 18 years with moderately to severely active disease. There are some significant safety concerns including the risk of serious infection, tuberculosis infection, infusion related reactions, neutropenia and thrombocytopenia. Significant pharmacovigilance would be required if approval is granted for pJIA. This would include vigilance for opportunistic infections, malignancy and cardiovascular AEs.

First round benefit-risk assessment

First round assessment of benefits

The benefits of TCZ in the proposed usage are:

- Significant rates of clinically meaningful JIA ACR responses (JIA ACR50, 70 and 90) were seen in the first 16 weeks of treatment with TCZ in the Cherish Study, as well as for extended periods of treatment in Studies MRA318JP and MRA319JP.
- The Cherish Study met its primary endpoint of a statistically significant and clinically meaningful lower rate of JIA ACR30 flare at Week 40 relative to Week 16 in TCZ treated patients (25.6%) compared to placebo subjects (48.1%; p=0.0024).
- Higher proportion of patients treated with ongoing TCZ versus placebo from Weeks 16 to 40 in the Cherish Study obtained JIA ACR30, 50, and 70 responses at Week 40.
- The Cherish Study showed that patients who were not receiving concurrent MTX and who had prior exposure to biologic DMARD achieved lower efficacy outcomes than those not in these subgroups of interest, but the differences were independent of TCZ treatment.
- A potential reduction in CS exposure in children with pJIA secondary to adequate disease control with TCZ (as observed in Study MRA319JP).
- TCZ offers an alternative treatment strategy for patients with moderately-severely active pJIA, which currently has limited treatment options and a significant unmet therapeutic need.

First round assessment of risks

The risks of TCZ in the proposed usage are:

- TCZ treatment carries an increased risk of infections: including serious infections. While most infections are mild and self limiting, it is likely TCZ therapy will lead to cases of serious infections and potentially death. No deaths were reported in the studies; however post-marketing experience has identified deaths with infection as a contributing factor.
- Increased risk of opportunistic infections, in particular tuberculosis, was observed in the pivotal Cherish Study.
- TCZ carries a risk of infusion related reactions (17.6% of 188 patients in the Cherish Study).
- TCZ is given by IV infusion and IV access in children can be difficult and lead to procedure related complications. Children can also develop significant psychological distress as a result of repeat attempts at IV access, and experience disruptions to social functioning (for example, school absenteeism) to attend IV infusion centres for ongoing care.
- Changes in haematological parameters, in particular neutropenia and thrombocytopenia, were seen in the studies involving pJIA patients. These were of no clinical significance to the majority of subjects in the studies, but some individual patients develop clinically significant haematological abnormalities.
- Changes in lipid profiles were identified which were not clinically relevant during the study period. The significance of the long term impact of the alterations seen in the lipid profile in children is not known and remains a potential long-term risk.
- Sufficient numbers of treated patients with long-term (multi-year) follow-up has not been achieved. This may be important for issues such as malignancy development and cardiovascular disease.

First round assessment of benefit-risk balance

The benefit-risk balance of TCZ in the target population of subjects aged 2-18 years with active pJIA is favourable. TCZ is administered by IV infusion every four weeks and the sponsor has proposed a dose of 8 mg/kg for those with a BW ≥ 30 kg, and a dose of 10 mg/kg in children with a BW < 30 kg. This dosing regimen has been justified in this submission, based primarily on the results of the single pivotal Cherish Study. In addition, the sponsor request to use TCZ as either monotherapy or in combination with MTX has been justified in this submission.

List of questions

Pharmacokinetics

1. Could the sponsor please comment on why actual BW versus BSA was chosen as the dose determining variable in the pivotal Cherish Study when the PopPK analysis indicates that BSA was the most significant covariate in explaining the moderate inter-patient variability in drug CL and peripheral (Vd)?
2. Could the sponsor please provide a detailed description of why 62 (2.3% of 2631) serum TCZ concentration samples were excluded from the PopPK dataset for the Cherish Study?

Pharmacodynamics

· No questions.

Efficacy

3. Could the sponsor please provide an update (if available) on the efficacy data collected in Part III of the Cherish Study?

Safety

4. Could the sponsor please provide an update (if available) on the safety data collected in Part III of the Cherish Study?
5. Could the sponsor please present the safety data for Parts I and II of the Cherish Study in a tabular format which identifies those AEs which were considered related to study treatment?

First round recommendation regarding authorisation

The evaluator recommended acceptance of the sponsor's proposed extension of indication for TCZ to include the treatment of pJIA subject to the following conditions:

· Satisfactory response to the questions raised in Clinical Questions,

· Refinement of the indication wording to include "moderately-severely active pJIA" (as per the studied populations),

· Implementation of an Australian specific RMP,

· Provision of the final clinical study report for Part III of the Cherish Study to the TGA as soon as possible. The final clinical study report should be submitted for formal evaluation as part of a Category 1 submission.

· Provision of regular Periodic Safety Update Reports (PSURS) as a condition of registration.

Second round evaluation of clinical data submitted in response to questions

The sponsor's response to further information requested by the TGA dated 1 March 2013 addresses six questions that were raised in the first round clinical assessment. Each of these responses will be assessed in order.

Clinical Question 1: Please comment on why actual BW versus BSA was chosen as the dose determining variable in the pivotal Cherish Study when the PopPK analysis indicates that BSA was the most significant covariate in explaining the moderate inter-patient variability in drug CL and peripheral Vd?

The sponsor concurs that of the four body size parameters (BSA, BMI, weight and height) assessed in the PopPK analysis using data from the Cherish Study, BSA was shown to be the most statistically significant covariate on TCZ CL and peripheral Vd. Analysis shows that the four body size parameters are highly correlated with each other, and the sponsor hypothesises that all of these covariates have similar relationships with the key PK parameters of interest (in particular, TCZ CL). The sponsor also asserts that dosing by BSA is not familiar to rheumatologists, and therefore has an increased propensity to dosing error in clinical practice than dosing by BW. The evaluator does not concur with the later part of the opinion as the sponsor should provide clinicians with the appropriate

education to optimise the use of therapy as part of good quality use of medicines principles.

Clinical Question 2: Please provide a detailed description of why 62 (2.3% of 2631) serum TCZ concentration samples were excluded from the PopPK dataset for the Cherish Study?

The sponsor states that the reasons for excluding 62 serum TCZ concentrations (2.3% of 2631 samples) from the PopPK dataset include: peak concentration too low, mid-concentration lower than trough concentration, trough concentration too high and inconsistent PK profile. Given the small overall number of anomalous samples in the total dataset, and the quality of the goodness-of-fit plots for various PK parameters, the proposed population PK model for TCZ in children with active pJIA is an acceptable and reliable result.

Clinical Question 3: Please provide an update (if available) on the efficacy data collected in Part III of the Cherish Study?

The sponsor states that the last patient is scheduled to complete Part III of the Cherish Study in January 2013, and they plan to submit a clinical study report, including efficacy data, to regulatory authorities in the fourth quarter of 2013.

Clinical Question 4: Please provide an update (if available) on the safety data collected in Part III of the Cherish Study?

The sponsor states that the last patient is scheduled to complete Part III of the Cherish Study in January 2013, and they plan to submit a clinical study report, including safety data, to regulatory authorities in the fourth quarter of 2013.

Clinical Question 5: Please present the safety data for Parts I and II of the Cherish Study in a tabular format which identifies those AEs which were considered related to study treatment?

The sponsor has presented an analysis of treatment related AEs by TCZ treatment group (each of the three TCZ dose groups [TCZ 8 or 10 mg/kg for those with BW ≤30 kg; and TCZ 8 mg/kg for those with BW >30 kg]), as well as a pooled TCZ treatment AE profile for the all exposure safety population involved in the Cherish Study. Data regarding the placebo treatment group in the Study's Part II withdrawal phase was excluded from the data presentation making it impossible to determine a treatment related AE difference between placebo and TCZ therapy. The determination of relationship between study drug and AE was assessed by the study investigator, and appears to be inconsistently applied. For example, commonly occurring infections such as nasopharyngitis and pneumonia were either equally, but often more frequently not attributed to active treatment. Furthermore, for the individual TCZ dose groups, the small patient numbers make it difficult to conclude any statistically significant differences (that is, insufficient statistical power). The incidence and type of treatment related AEs showed a similar pattern to that observed in the overall AE assessment (irrespective of relationship to study medication). The major finding of this ancillary analysis was that patients with a BW > 30 kg were observed to have a higher frequency of treatment related infections (25.0%; 47/188) compared to TCZ treatment patients weighing ≤ 30 kg (14.3% [4/28] for TCZ 10 mg/kg and 23.5% [8/34] for TCZ 8 mg/kg). No other specific pattern of TCZ related AE was observed.

Clinical Question 6: Please comment on the recommendation to amend the wording in the clinical trials and indication sections to reflect the baseline disease activity (that is, moderately to severely active disease at baseline) of the recruited population in the pivotal Cherish Study?

The sponsor accepts the suggested amendment to the indication wording to include "moderate or severe" disease activity. At baseline in the pivotal Cherish Study, patients had active disease with the mean (and SD) number of active joints being 20.3 (14.3), mean patient/parent global assessment being 52.9 mm (25.0), mean physician global

assessment being 61.4 mm (20.7), mean Childhood Health Assessment Questionnaire – Discomfort Index (CHAQ-DI) score was 1.39 (0.74) and mean Erythrocyte Sedimentation Ratio (ESR) being 34.8 mm/hr (25.5).

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of TCZ in the proposed usage are unchanged.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of TCZ in the proposed usage are unchanged.

Second round assessment of benefit-risk balance

Upon assessment of the available data, the benefit-risk balance of TCZ, given in the proposed posology for less than one year of therapy, is favourable. However, the final clinical study report for Part III of the Cherish Study (in particular, the safety data) should be submitted for formal evaluation before a final recommendation can be made.

Second round recommendation regarding authorisation

Although the data submitted thus far demonstrates a favourable, short-term benefit-risk assessment for TCZ in the proposed usage, the evaluator would not recommend acceptance of the sponsor's proposed extension of indication for TCZ to include the treatment of pJIA at this point in time. The data pertaining to the final clinical study report for Part III of the Cherish Study should be formally evaluated. As the request for extension of treatment indication is based on one pivotal study involving less than 200 children in total, it is important to evaluate the two year data (Part III) in addition to the currently submitted 40 Week data (Parts I and II). The two year follow-up period provides an appropriate time frame and overall patient exposure dataset to assess safety outcomes over the short and medium term. The TGA has adopted the EU guideline CPMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis" (effective 26 June 2009) which advises that an observation period of at least 12 months is required to assess clinical safety and identify relevant AEs in the paediatric population, particularly when the profile of risks may not be consistent with the adult population experience. The same guideline proposes that for disease modifying therapies in JIA, study duration of at least six months is necessary for evaluating the maintenance of efficacy. The minimum standard for determination of efficacy has been met by the current submission. However, for the safety assessment, the current submission does not meet guideline criterion.

TCZ has marketing approval in Australia for the treatment of active sJIA based on a smaller subject number (n<100) and shorter duration of follow-up (12 weeks) in the single pivotal study. However, in contrast to pJIA, sJIA is of very low prevalence (10-15% of all JIA cases), has a distinctive auto-inflammatory pathogenesis that is mechanistically related to cytokine activation (especially IL-6), and a high rate of disease progression without effective treatment. There is scope within the relevant JIA regulatory guideline for accepting a lower volume of supporting evidence in such circumstances (that is, rare conditions with a significantly high unmet clinical need). Polyarticular JIA has a relatively higher prevalence (approximately 50% of all JIA cases), and there are several currently

approved treatment options in Australia for moderately to severely active pJIA including NSAIDs, CS, non-biological DMARDs (mainly MTX) and two anti-TNF therapies. As such, the safety data for Part III of the single pivotal Cherish Study should be reviewed as part of the submission for extension of TCZ indication to include the treatment of active pJIA. This viewpoint is consistent with the principles outlined in the relevant regulatory guideline (CPMP/EWP/422/04).

If this submission is approved, a recommended condition of registration is the provision of regular PSURs by the sponsor.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan identified as EU-RMP Version: 13.0, dated May 2012, with an Australian Specific Annex (ASA) Version: 1.0, dated 7 August 2012, which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the clinical aspects of the Safety Specification by the TGA's Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is at Table 3.

Table 3: Summary of Ongoing Safety Concerns

Category	Safety Concern	Comment
Important Identified Risks	Serious infection	Observed with TCX and other biological DMARDs
	Complications of diverticulitis (including GI perforation)	Risk increased with RA, use of CS and/or NSAIDs. Observed with TCZ and other biological DMARDs
	Serious hypersensitivity reactions	Observed with TCZ and other biological DMARDs
Important Potential Risks	Neutropenia	Observed with TCZ and other biological DMARDs
	Thrombocytopenia	Observed with TCZ and other biological DMARDs
	Elevated hepatic transaminases	Observed with TCZ and other biological DMARDs. Elevated bilirubin (essentially indirect) observed with TCZ; linked to Gilbert's variants; no clinical consequences
	Elevated lipids	Observed with TCZ

Category	Safety Concern	Comment
	Elevated bilirubin (essential indirect)	Observed with TCZ; linked to Gilbert's variants; no clinical consequences
	Immunogenicity	Observed with TCZ; clinical relevance needs further investigation
	Malignancies	Based on increased risk in RA and with other biological DMARDs; no imbalance noted for TCZ
Important Potential Risks cont.	Demyelinating disorders	Based on increased risk with other biological DMARDs; two 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 TCZ treatment.
	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 TCZ; 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 or effect or concentration, & dosage adjustment, as standard clinical practice. Risk applies at initiation and withdrawal of TCZ treatment
Important missing information	Elderly	No clinical evidence of increased risk; no difference in PK
	Paediatric patients	Paediatric program ongoing (PIP approved)

Category	Safety Concern	Comment
	Effects during pregnancy	Use in pregnancy not recommended
	Hepatic impairment	Caution to be exercised in this subgroup; TCZ not subject to hepatic metabolism
	Renal impairment	No dose adjustment required; TCZ not subject to renal elimination. No effect of mild renal impairment noted with TCZ. No formal study in patients with mild to moderate renal impairment.
	Combination of biologics	Study ongoing: rituximab + TCZ
	Vaccinations	Efficacy of proteinaceous and polysaccharide vaccines to be studied in comcomitant use with TCZ.
	Increased mortality in the Japanese PMS compared to clinical study population	Observation likely to reflect population being exposed. Patients are elderly with significant concurrent medical disease and multiple concomitant medications.

Office of Product Review (OPR) reviewer comment:

The above ongoing safety concerns are the same as those previously accepted for Actemra.

Pursuant to the evaluation of the clinical aspects of the SS, it is considered that the specified ongoing safety concerns are acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The only changes to the previously accepted pharmacovigilance activities are the following:

- For the important missing information: 'Paediatric patients' & 'Concomitant Use of Vaccines', the ongoing Tender Study to evaluate the efficacy and safety of TCZ in patients with active sJIA has been updated to include a Part III (three year single-arm OLE) designed to provide long term safety data and study the effect of inactivated vaccine (influenza) in the paediatric population. A protocol for this study dated 7 January 2011 was provided in Annex 5 of the EU-RMP and a clinical study report is expected to be submitted in February 2015. In addition this Part III has an 'Optional Alternative Dosing Schedule': Patients who meet specific clinical criteria will have the option of decreasing study drug administration frequency to every three weeks, then every four weeks, then off TCZ at certain time points during Part III of the study.

- For the important missing information: 'Paediatric patients', updated details of the Pharmachild JIA registry have now been provided. The primary objectives of this registry, conducted by the Paediatric Rheumatology International Trials Organisation, are to assess the long-term safety of MTX and biologic agents in JIA. The sponsor reports that enrolment is planned to start in 2012 and preliminary analyses are planned every year with analysis of AEs incidence rate. Rate comparison will be performed after enrolment of 50% of the estimated sample and at the end of the study. The sponsor's correspondence dated 1 March 2013 confirmed that the protocol is currently under development and will be submitted to the EU Committee for Medicinal Products for Human Use (CHMP) by the second quarter of 2013.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP)

The sponsor should provide an assurance that the draft protocol for the Pharmachild JIA registry, which is to be submitted to the CHMP by the second quarter of 2013, will also be submitted to the TGA for review once it becomes available and included in Annex 5 of the EU-RMP when this document is next updated.

Risk minimisation activities

It would appear that the sponsor has concluded that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important identified risk: 'Serious hypersensitivity reactions' for which additional risk minimisation activities are also proposed.

OPR reviewer comment:

There appears to be no change to the previously accepted risk minimisation activities proposed for these products. However, it is noted that the submitted EU-RMP states that additional risk minimisation activities in the form of an alert card supported by more detailed information for the prescribing physician are required for the important identified risks: 'Serious infection' & 'Complications of diverticulitis (including GI perforation)'. The sponsor had previously provided justification for why routine risk minimisation activities are sufficient for the important identified risks: 'Serious infection' & 'Complications of diverticulitis (including GI perforation)' and the important potential risk: 'Neutropenia' and this was accepted. Nevertheless the sponsor should explicitly state in the 'Australian Risk Management Plan' of the ASA that no additional risk minimisation activities are undertaken in Australia for the important identified risks: 'Serious infection' & 'Complications of diverticulitis (including GI perforation)' rather than the phrase: *"except no Alert Card".*

Risk minimisation plan

Routine risk minimisation activities will comprise labelling, including PK data, special warning and precaution statements, instructions for use and/or notification of undesirable effects for all the specified ongoing safety concerns.

Additional risk minimisation activities are proposed for the important identified risk: 'Serious hypersensitivity reactions'.

The sponsor's correspondence dated 1 March 2013 has also identified how the Risk Minimisation Plan recommendations made in a previous RMP Evaluation report for Actemra have been addressed.

OPR reviewer comment:

The sponsor has stated that sJIA patients are not permitted to receive Actemra under the ACTiv program and will only receive infusions in hospital. The sponsor should provide a similar assurance that pJIA patients will not be permitted to receive Actemra under the ACTiv program and will only receive infusions in hospital.

In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.

In regard to the proposed routine risk minimisation activities, the draft Consumer Medicine Information (CMI) is considered satisfactory.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft PI and CMI documents should NOT be revised until the Delegates Overview has been received:

1. The sponsor should provide an assurance that the draft protocol for the Pharmachild JIA registry, which is to be submitted to the CHMP by the second quarter of 2013, will also be submitted to the TGA for review once it becomes available and included in Annex 5 of the EU-RMP when this document is next updated.
2. There appears to be no change to the previously accepted risk minimisation activities proposed for these products. However, it is noted that the submitted EU-RMP states that additional risk minimisation activities in the form of an alert card supported by more detailed information for the prescribing physician are required for the important identified risks: 'Serious infection' & 'Complications of diverticulitis (including GI perforation)'. The sponsor had previously provided justification for why routine risk minimisation activities are sufficient for the important identified risks: 'Serious infection' & 'Complications of diverticulitis (including GI perforation)' and the important potential risk: 'Neutropenia' and this was accepted. Nevertheless the sponsor should explicitly state in the 'Australian RMP' of the ASA that no additional risk minimisation activities are undertaken in Australia for the important identified risks: 'Serious infection' & 'Complications of diverticulitis (including GI perforation)' rather than the phrase: *"except no Alert Card".*
3. The sponsor has stated that sJIA patients are not permitted to receive Actemra under the ACTiv program and will only receive infusions in hospital. The sponsor should provide a similar assurance that pJIA patients will not be permitted to receive Actemra under the ACTiv program and will only receive infusions in hospital.
4. In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.
5. In regard to the proposed routine risk minimisation activities, the draft CMI is considered satisfactory.

VI. Overall conclusion and risk/benefit assessment

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

Background

TCZ is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 (gamma 1) subclass, directed against the IL-6 receptor.

TCZ binds specifically to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit sIL-6R- and mIL-6R-mediated signalling. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including RA. In clinical studies with TCZ, rapid decreases in CRP, ESR and serum amyloid A were observed.

Actemra was first approved in Australia in May 2009 for the treatment of moderate to severe active RA in adult patients. In October 2010 the indication was extended to include inhibition of the progression of joint damage, as measured by X-ray, when given in combination with MTX. In October 2011 the indication was further extended to include sJIA in patients 2 years of age and older.

In August 2010, a fatal case of anaphylaxis following TCZ infusion was notified to the TGA. This resulted in a safety-related update of the Actemra PI and the development of a safety protocol for administration of the drug in dedicated infusion clinics (ACTiv program), based on advice received by the sponsor from medical organisations with an interest in the emergency management of anaphylaxis. However it was a specific condition of registration attached to the delegate's approval of the sJIA indication that administration of TCZ for the paediatric indication "*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 number of children"*.

There is one specific TGA adopted EU guideline which may be relevant to this submission, in addition to paediatric-specific and general guidelines:

- CPMP/EWP/422/04. Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis. Published: TGA Internet site. Effective: 26 June 2009
- CPMP/ICH/2711/99. Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. Published: TGA Internet site. Effective: 19 April 2001
- EMEA/CHMP/PEG/194810/2005. Reflection Paper: Formulations of Choice for the Paediatric Population. Published: TGA Internet site. Effective: 29 June 2009
- CHMP/EWP/147013/2004. Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (corrigendum). Published: TGA Internet site. Effective: 24 August 2009

Quality

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

Nonclinical

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

Clinical

Overview of data

The clinical evaluator reviewed the submitted data, which included:

- One Phase III pivotal study (The Cherish Study or Study WA19977), which included clinical PK and PD sub-studies and one PopPK sub-study
- One Phase III supportive open-label Study (MRA318JP) with an extension phase (MRA319JP), which included clinical PK and PD sub-studies and one PopPK sub-study
- One post-marketing observational cohort study (ML21939, also known as JPMS) providing safety data
- One summary of clinical pharmacology studies
- One summary of clinical efficacy
- One integrated summary of clinical safety

The clinical evaluator initially determined that the data demonstrates a favourable short-term benefit-risk assessment for TCZ however does not recommend approval until the final clinical study report for the Cherish Study is evaluated (available June 2013). The evaluator partly based this decision on the EU guideline CPMP/EWP/422/04 " Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis" (effective 26 June 2009) which advises that:

> *Whenever there are no data in the adult population that are consistent with the profile observed in paediatric patients an observation period of not less than twelve months is required to assess clinical safety and identify relevant adverse reactions in the paediatric population.*

The final Cherish Study clinical study report (CSR) was submitted on 21 June 2013 and based on demonstrating maintenance of efficacy and no new safety concerns, the evaluator has subsequently recommended approval.

The benefits noted by the evaluator included:

- Early onset of efficacy – 50% of responders at Week 16 responded by Week 2
- 89.4% of patients achieved ≥ JIA ACR30 response at Week 16 (76.5% of patients <30 kg on TCZ 8 mg/kg, 88.6% of patients <30 kg on TCZ 10 mg/kg, and 93.3% of patients ≥30 kg on TCZ 8 mg/kg)
- significantly fewer patients receiving TCZ experienced a JIA ACR30 flare at Week 40 compared with those receiving placebo (25.6% vs. 48.1%, p=0.0024)
- lower rate of flare in TCZ-treated patients on baseline MTX (19%) than those not receiving MTX (53%)
- lower rate of flare in TCZ-treated patients who were DMARD naive (16%) than those previously exposed to biologic DMARDs (44%)
- JIA ACR30/50/70 improvement at Week 40 significantly higher in patients receiving TCZ compared with those receiving placebo
- Significant improvements in number of active joints, physician's global assessments and Pain VAS
- Maintenance of efficacy through Week 104 was demonstrated for each of the JIA ACR30/50/70/90 response rates in the OLE, and were similar for the continuous TCZ-treated subgroup and the placebo-treated subjects (in Part II) who had re-initiation of TCZ
- The improvement in JIA ACR core components previously reported in the Week 40 CSR was at least maintained through Part III of the study

The concerns noted by the evaluator included:

- TCZ treatment carries an increased risk of infection, with the potential for serious infection and death. No deaths were reported in the studies, however post-marketing experience has identified deaths with infection as a contributing factor
- Increased risk of opportunistic infections, in particular tuberculosis, was observed in the pivotal Cherish Study
- TCZ carries a risk of infusion related reactions (17.6% of 188 patients in the Cherish Study
- TCZ is given by IV infusion and IV access in children can be difficult, lead to procedure related complications and develop psychological distress
- Changes in haematological parameters, in particular neutropaenia and thrombocytopenia, were seen in the studies involving pJIA patients. These were of no clinical significance to the majority of subjects in the studies, but some individual patients developed clinically significant haematological abnormalities
- Changes in lipid profiles were identified which were not clinically relevant during the study period. The significance of the long term impact of the alterations seen in the lipid profile in children is not known and remains a potential long-term risk

Pharmacology

The Cherish study

The PK/PD data were collected as part of the pivotal Cherish Study and supportive open label studies (MRA318JP and MRA319JP).

Cherish Study (WA19977): The TCZ serum concentrations collected pre- and post-dose in Parts I (initial 16 weeks of treatment) and II (up to Week 40) of the Cherish Study were used to develop a PopPK model for patients with pJIA. The serum concentration-time course for TCZ in patients with active pJIA was best described by a two-compartment disposition PK model with parallel first-order and Michealis-Menten elimination kinetics. The PopPK parameters were: CL - 5.8 mL/hr, central Vd - 1.98 L, peripheral Vd - 2.10 L, and maximum elimination rate - 6.58 mg/day. BSA was significantly correlated with variability in CL and peripheral Vd, while height was significantly correlated with central Vd. Age, gender, race and creatinine CL were not found to have any influence on the PK of TCZ.

The key model computed TCZ parameters in Part I of the study are shown in Table 4 below, with results from studies in sJIA and adult patients with RA provided for comparison. For pJIA patients in the Cherish Study, TCZ 8 mg/kg q4w in subjects with a BW ≥30 kg, and the 10 mg/kg q4w dose in patients with a BW <30 kg resulted in similar TCZ PK exposure parameters to those observed in adult patients with active RA dosed with TCZ 8 mg/kg q4w. Children with sJIA appear to require a higher dose of TCZ given more frequently (8 or 12 mg/kg every two weeks (q2w)) which reflects the increased systemic activity of their illness.

Table 4: Comparison of PK exposure parameters in pJIA, sJIA and adult RA patients

Population, Study	Dose Regimen	Mean ± Standard Deviation C_{max} (µg/mL)	C_{min} (µg/mL)	AUC [a] (µg·day/mL)
pJIA, Study WA19977 Part I, n = 177				
	8 mg/kg q4w (BW ≥ 30kg)	182 ± 37	7.49 ± 8.20	1231 ± 361
	10 mg/kg q4w (BW < 30kg)	175 ± 32	2.35 ± 3.59	968 ± 254
	8 mg/kg q4w (BW < 30 kg)	140 ± 25	0.95 ± 2.37	702 ± 218
pJIA, Study MRA318JP, n = 19				
	8 mg/kg q4w	145 ± 34.7	4.88 ± 4.68 [b]	1054 ± 280 [c]
sJIA, Study WA18221, n = 75				
	8 mg/kg q2w (BW ≥ 30kg)	226 ± 54.5	54.5 ± 20.7	1337 ± 409 [b]
	12 mg/kg q2w (BW < 30kg)	263 ± 54.1	60.5 ± 25.5	1346 ± 426 [b]
Adult RA, Studies WA17822, WA17824, WA18062, WA18063, n = 1820				
	8 mg/kg q4w	187 ± 85	8.6 ± 8.9	1417 ± 613
	4 mg/kg q4w	88 ± 41	1.4 ± 1.9	538 ± 239

All PK parameters were PK model-computed, except for MRA318JP where non-compartmental analysis was used; BW: body weight; [a] AUC over dosing interval, i.e., $AUC_{2\ weeks}$ for sJIA (q2w dosing) and $AUC_{1\ weeks}$ for pJIA and adult RA (q4w dosing); week 12; [c] AUC_{inf} for first dose.

JIA ACR30/50/70/90 non-responders in Part I of the Cherish Study had a lower exposure to TCZ than responders, but higher levels of response (JIA ACR50/70/90 versus JIA ACR30) were not associated with higher levels of exposure.

Patients with the lowest quartile of drug exposure to TCZ in Part II of the Cherish Study had the lowest incidence of overall AEs and of the two most common types of AEs (infections and GI disorders).

In Part III of the Cherish Study there was no apparent correlation between drug exposure quartile and efficacy or AEs with the exception of GI AEs which had a higher frequency in the highest quartile.

In Part III of the Cherish Study there was no apparent correlation between drug exposure quartile and efficacy or AEs with the exception of GI AEs which had a higher frequency in the highest quartile.

Studies MRA318JP/MRA319JP

The TCZ serum concentrations collected pre- and post-dose in study MRA318JP were used to develop a PopPK model for patients with pJIA to examine the relationship between PK, BW, and clinical efficacy. Exposure to TCZ appears to decrease with decreasing BW, particularly below a BW of ~30 kg. In contrast, in patients with a BW >30 kg exposure appeared to be more or less independent of BW. Dosing had to be increased to 10mg/kg in patients <30 kg to obtain a similar TCZ exposure to that of patients ≥ 30kg receiving 8mg/kg. The lower TCZ exposure was associated with lower efficacy: JIA ACR50 88% versus 100% and JIA ACR70 38% versus 80% in patients <30 kg and ≥30 kg, respectively.

No clear relationship was found between serum trough TCZ concentration and clinical efficacy indices (for example, active joint count) in the extended treatment phase (MRA319JP).

Some of the PD findings noted by the evaluator include:

- a decrease in serum inflammatory markers (CRP and ESR) was observed within two to four weeks of first TCZ administration and remained low whilst on TCZ treatment through to Week 40
- mean serum IL-6 concentrations increased after each TCZ infusion (greatest with first infusion), but generally remained low thereafter
- mean values for sIL-6R increased rapidly (one to four) following TCZ infusion and remained constant thereafter for extended periods of follow-up (at least 40 weeks)
- In the pivotal Cherish Study, patients with a BW <30 kg who received TCZ 8 mg/kg (n=11), recorded mean sIL-6R concentrations from Weeks 12 to 40 that were approximately half the value of the other two TCZ dose groups. This suggests that the higher dose of TCZ (10 mg/kg) may be required in patients with a BW <30 kg to achieve the optimal PD response equating to dosing with TCZ 8 mg/kg in patients with a BW >30 kg.

Efficacy with regard to the treatment of pJIA

Efficacy data were presented from the pivotal Cherish Study and one supportive Study MRA318JP with an extension Phase MRA319JP.

The Cherish Study was a two-year three-part Phase III study to evaluate the efficacy and safety of TCZ in patients with active pJIA. It was conducted at 58 centres in 15 countries. Part I consisted of a 16-week active TCZ treatment lead-in period, Part II was a 24-week (or time to flare) randomised double-blind placebo-controlled withdrawal period, and Part III was a 64-week open-label period beginning at Week 40 (or once a patient entered escape therapy with TCZ) to examine the long-term safety and efficacy of TCZ.

The overall study design is consistent with regulatory guidelines in the USA and EU. The active treatment, then withdrawal study design reduces the risk to paediatric patients of prolonged, untreated active disease, while maintaining data integrity because of the randomisation process leading into Part II.

Patients with a BW <30 kg were randomised in a 1:1 ratio to either TCZ 8 mg/kg or 10 mg/kg IV infusion q4w, while all patients with a BW ≥30 kg received TCZ 8 mg/kg IV infusion q4w. Efficacy was assessed using the JIA ACR response measure. Patients who achieved at least a 30% improvement (that is, a JIA ACR30 response) at Week 16 compared to baseline were eligible to enter Part II. In Part II, patients were randomised in a 1:1 ratio to treatment with TCZ (at the same dose level as in Part I) or to placebo. Randomisation was stratified by concomitant MTX use and concomitant oral CS use. Patients who developed a JIA ACR30 flare relative to Week 16 qualified for escape therapy with TCZ at the same dose as in Part I, but could also receive intra-articular CS injections, or a change in concomitant medications (for example, oral prednisone could be increased up to a maximum of 10 mg/day or 0.2 mg/kg/day, whichever was less). In Part III, patients originally randomised to the TCZ 10 mg/kg dose could have the dose reduced to 8 mg/kg if the patient's BW had increased to ≥30 kg and was at least 5 kg above the baseline BW for three consecutive visits.

Eligibility criteria included: age ≥ 2 years but < 17 years; and meeting the ILAR criteria for the three subtypes of pJIA (that is, RF positive or negative pJIA, or extended oligoarthritis for at least six months). The pJIA had to be clinically active at screening with at least five active joints (swollen and/or limited movement), including at least three active joints having limitation of motion (LOM) at baseline. Patients were required to have a history of either inadequate response to or intolerance of MTX. MTX could be continued at a stable dose of 10-20 mg/m^{2}in those receiving it for at least 12 weeks prior to study entry. Continuing treatment with NSAID and low dose prednisone (no more than 10 mg/day or 0.2 mg/kg/day, whichever was less) was also permitted if the patient had received a

stable dose for the two to four weeks prior to baseline. Prior biological DMARD therapy was allowed as long as the therapy had been ceased for at least five half-lives prior to enrolment. The number of patients with prior biologic DMARD exposure was not to exceed 30% of the total number of study participants. If appropriate, female patients were required to use contraception.

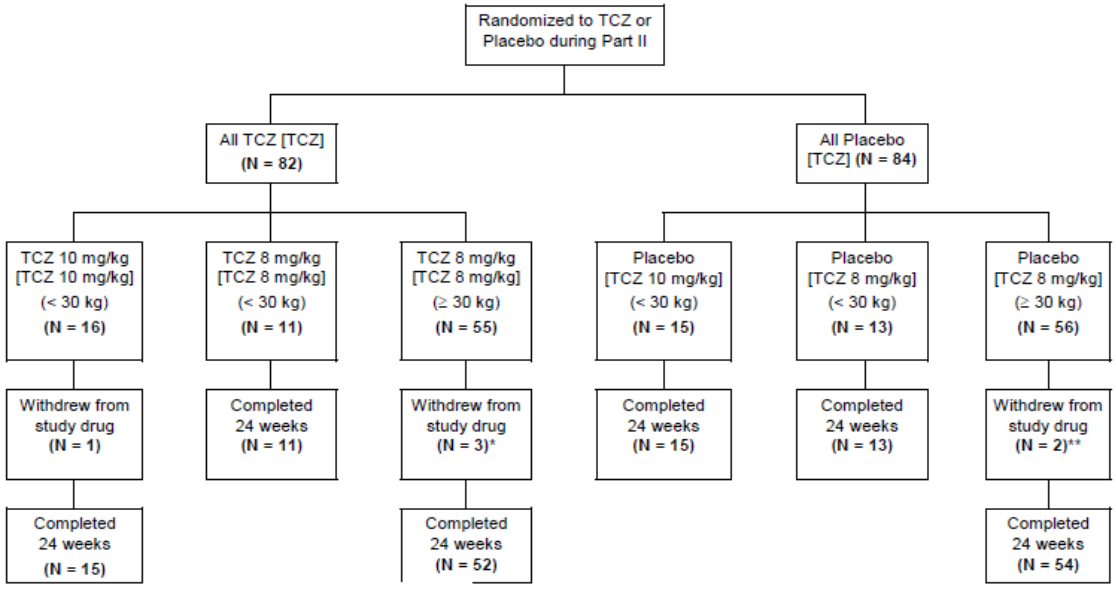
Exclusion criteria comprised four domains and patients meeting any one of the below criteria were excluded:

- General – such as wheelchair bound, bedridden, or having little or no ability to self-care;
- Co-morbidities – active infection, history of recurrent infection, immunodeficiency, history of reactivated or recent onset systemic infection with Epstein Barr virus or herpes zoster, asthma requiring the use of oral or parenteral CS for more than two weeks in the six months prior to baseline, active uveitis within 12 weeks of baseline, history of any GI disorder, congenital or valvular heart disease, evidence of latent or previously treated tuberculosis, and any history of malignancy;
- Baseline laboratory results – haemoglobin <9.0 g/dL, total WCC <5000/mm^3, neutrophil count <2500/mm^3, Platelet count <150,000/mm^3, ALT or AST > 1.5 upper limit of normal (ULN), total bilirubin >1.3 mg/dL, serum creatinine > 1.5 ULN for age and gender, and positive hepatitis B surface antigen or hepatitis C antibody;
- Past treatments – prior treatment with any conventional DMARD (other than MTX); IV immunoglobulin within the last four weeks; treatment with leflunomide within the last three months; and live or attenuated vaccines within four weeks of randomisation.

A total of 218 patients were screened and 188 were randomised to TCZ in Part I: 119 with a BW ≥30 kg received TCZ 8 mg/kg, 34 with a BW <30 kg received TCZ 8 mg/kg, and 35 with a BW <30 kg received TCZ 10 mg/kg. Part I of the trial was completed by 166 patients (88%): 31/35 (89%) <30 kg on TCZ 10 mg/kg, 24/34 (71%) <30 kg on TCZ 8 mg/kg, and 111/119 (93%)≥30 kg on TCZ 8 mg/kg.

Of the 166 patients entering Part II of the trial, 82 were randomised to TCZ (55 with a BW ≥30 kg received TCZ 8 mg/kg, 11 with a BW <30 kg received TCZ 8 mg/kg, and 16 with a BW <30 kg received TCZ 10 mg/kg) and 84 to placebo (53 with a BW ≥30 kg and 28 with a BW <30 kg). Part II of the trial was completed by 160 patients (96% of those entering Part II, 85% of those randomised to Part I) (see Figure 1 below). Part III of the trial was completed by 155 patients.

Figure 1: Participant flow in Part II of Cherish Study



Protocol violations - a site in Spain failed to perform the joint assessments in a blinded, independent manner as required by the protocol. This affected 19 of 67 study visits for six subjects. Corrective and preventive actions were taken at the site, and it was verified that no other site was similarly breaching this protocol requirement. It does not appear that analyses were performed with and without these subjects, and it is unclear if this would have affected the results.

Baseline characteristics for Part I of the study were similar between the treatment groups in patients with a BW <30 kg, with those with a BW ≥30 kg being on average older (13.1 versus 7.2 years), having a longer duration of disease (4.7 versus 3.4 years), and a higher percentage prior biologics use (39% versus 20%). Across the three treatment groups, the mean age was 11 years (range 2-17 years), 77% were female, 80% were Caucasian and the mean duration of disease was 4.2 ± 3.7 years. The majority of patients were RF-negative at baseline (67%), with eight patients (4.3%) having no recorded RF status. Baseline disease characteristics were slightly different across the treatment groups. For example, patients <30 kg on TCZ 10 mg/kg had a numerically higher number of joints with active arthritis (23.9) or LOM (23.1), than patients ≥30 kg on TCZ 8 mg/kg (18.9 and 16.0, respectively), or patients <30 kg on TCZ 8 mg/kg (21.2 and 17.3, respectively). Other disease characteristics were comparable across the groups, with 79% on concurrent MTX, and 46% on concurrent CS at baseline. These characteristics were similar in patients continuing in Part II and Part III of the study.

The sample size was calculated to be 60 patients each in the TCZ and placebo groups in order to provide 80% power to detect a significant treatment difference (placebo 65% versus TCZ 35%) using a two-side significance test with $\alpha = 0.05$. This required recruitment of 185 subjects and assumed a JIA ACR30 response rate of 65% in Part I of the study.

All patients who received at least one dose of TCZ in Part I of the study were included in the intention-to-treat (ITT)-1 Population. The ITT-2 Population consisted of all patients who were randomised into Part II and who received at least one dose of study medication (TCZ or placebo). Because the study had multiple endpoints, a hierarchical testing strategy was employed to control for the Type I error rate. The primary and secondary endpoints were tested at the 5% significance level ($\alpha=0.05$) using a two-sided test. Secondary efficacy endpoints were tested in a fixed hierarchical sequence approach, if the primary endpoint was found to be statistically significant. Only if statistical significance was demonstrated in a higher-ranking endpoint were lower-ranking endpoints evaluated.

In Part I of the study, onset of efficacy was observed early, with 50% of responders at Week 16 achieving this outcome by Week 2. Overall, 89.4% patients achieved at least a JIA ACR30 response, with the response rate being slightly lower in patients <30 kg on TCZ 8 mg/kg (76.5%), compared with patients <30 kg on TCZ 10 mg/kg (88.6%) or patients ≥30 kg on TCZ 8 mg/kg (93.3%). This pattern of response was also seen across the JIA ACR50/70/90 endpoints (see Table 5 below).

Table 5: Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 16 (Cherish Study, ITT-I)

	TCZ 10 MG/KG (<30KG) (N=35)	TCZ 8 MG/KG (<30KG) (N=34)	TCZ 8 MG/KG (>=30KG) (N=119)	ALL TCZ (N=188)
Week 16				
n	35	34	119	188
JIA ACR30 Response	31 (88.6%)	26 (76.5%)	111 (93.3%)	168 (89.4%)
JIA ACR50 Response	28 (80.0%)	24 (70.6%)	104 (87.4%)	156 (83.0%)
JIA ACR70 Response	22 (62.9%)	14 (41.2%)	81 (68.1%)	117 (62.2%)
JIA ACR90 Response	11 (31.4%)	8 (23.5%)	30 (25.2%)	49 (26.1%)

Responders are patients who had a JIA ACR30/50/70/90 response (relative to Baseline) at the visit.
Patients who withdrew or for whom the endpoint could not be determined are classified as non-responders.
For treatment groups the body weight category at Baseline is indicated in ().

The primary efficacy endpoint was the proportion of patients who developed a JIA ACR30 flare (relative to Week 16) in the period from Week 16 up to and including Week 40 in Part II. The JIA ACR response is derived from six variables: parent/patient global assessment of overall well-being (range: 0-100), physician global assessment of disease activity (range: 0-100), number of joints with active arthritis, number of joints with LOM, ESR, functional ability determined by Childhood Health Assessment Questionnaire (CHAQ) - Disability Index (DI). In the Cherish Study, the patient was considered to have attained a JIA ACR30 response if three of the six core variables had improved by at least 30%, and no more than one of the other variables had worsened by more than 30%. The JIA ACR 30 index is a validated, internationally accepted disease activity measure in JIA. Significantly fewer patients receiving TCZ experienced a JIA ACR 30 flare at Week 40 compared with those receiving placebo (25.6% versus 48.1%, p=0.0024). There was no interaction between baseline CS use and JIA ACR30 flare, but those patients on baseline MTX receiving TCZ had a lower rate of flare (19%) than those not receiving MTX (53%). This was also observed in the group receiving placebo, with those on baseline MTX experiencing a lower rate of flare (39%) than those not receiving MTX (82%). In addition, the rate of JIA ACR30 flare in TCZ-treated patients who were DMARD naive was lower (16%) than in patients previously exposed to biologic DMARDs (44%). In the placebo group these rates were 36% and 78%, respectively. This most likely reflects a treatment-refractory subgroup of pJIA. Baseline RF status (positive/negative) had no effect on the rate of JIA ACR30 flare at Week 40 for either the active TCZ treatment or placebo group.

There were multiple secondary endpoints (see Table 6 below), with the first six also demonstrating the superiority of TCZ compared with placebo at Week 40.

Table 6: Overview of Efficacy Results at Week 40 (Study WA19977 Part II, ITT-2, CFB=change from baseline)

	Endpoint	All Placebo N=81	All TCZ N=82	Difference [a] [95% CI]	p-value
Primary Efficacy Endpoint					
1	Proportion of patients with JIA ACR30 flare (relative to week 16): n (%)	39 (48.1%)	21 (25.6%)	-0.21 [-0.35;-0.08]	0.0024
Secondary Efficacy Endpoints					
2	Proportion of patients with JIA ACR30 Improvement: n (%)	44 (54.3%)	61 (74.4%)	0.19 [0.05; 0.33]	0.0084
3	Proportion of patients with JIA ACR50 Improvement: n (%)	42 (51.9%)	60 (73.2%)	0.20 [0.06; 0.34]	0.0050
4	Proportion of patients with JIA ACR70 Improvement: n (%)	34 (42.0%)	53 (64.6%)	0.22 [0.07, 0.37]	0.0032
5	CFB in number of active joints: Adjusted Mean	-11.4	-14.3	-2.9 [-5.7;-0.1]	0.0435
6	CFB in Physician's global assessments VAS: Adjusted Mean	-35.2	-45.2	-9.9 [-16.5;-3.4]	0.0031
7	CFB in the pain VAS: Adjusted Mean	-22.3	-32.4	-10.2 [-17.6;-2.7]	0.0076
8	CFB in number of joints with limitation of movement: Adjusted Mean	-7.7	-9.5	-1.8 [-4.1;0.5]	**0.1229**

In Part III of the study, maintenance of efficacy through Week 104 was demonstrated for each of the JIA ACR30/50/70/90 response rates in the OLE, and were similar for the continuous TCZ treated subgroup and the placebo-treated subjects (in Part II) who had re-initiation of TCZ. Improvement in JIA ACR core components previously reported in the Week 40 CSR was maintained. Growth parameters (height, BMI) increased appropriately from baseline for all patients who received at least one dose of TCZ over the 104 weeks of study follow-up.

Studies MRA318JP and MRA319JP

Study MRA318JP was a supportive OLE study of the safety and efficacy of TCZ 8 mg/kg q4w conducted in five centres in Japan (n=19). The initial treatment phase was 12 weeks, followed by an OLE phase of 42 months (MRA319JP). Concurrent MTX use was not permitted in either of the MRA studies, in contrast to the majority of subjects (79%) involved in the Cherish Study.

The primary efficacy endpoint was JIA ACR30 response at Week 12. This was achieved by 94.7% (18/19) of patients. For those subjects who remained in the study, response rates were maintained for up to 168 weeks: 94.1% (16/17) at Week 24, 100% (17/17) at Week 48, 100% (16/16) at Week 96, and 100% (15/15) at Week 168.

Safety

Safety data were presented from the pivotal Cherish Study, the study conducted in Japan, MRA318JP/MRA319JP, and an observational cohort study (ML21939). In the Cherish Study, the median exposure to study medication at the data cut-off date of 4 November 2011 was 48 weeks (range 0.1 - 96.1), representing 184.4 PY of exposure. The majority (94%) of the 188 patients received all four TCZ infusions in Part I of the study, and 70% of the 82 patients received all six TCZ infusions in Part II. In the final Cherish Study CSR, the

median duration of exposure to TCZ for the all exposure group was 1.85 years, representing 307.0 PY of exposure.

In MRA318JP/MRA319JP, the median duration of treatment was 3.22 years (range: 0.35-3.53), representing 55.7 PY of exposure.

The Cherish study

AE data were collected up to Week 40 (data cut-off-date of 4 November 2011), and beyond for the open label period. Of note, the AE profile for patients on placebo during the Part II treatment withdrawal phase was not presented; therefore no comparison of placebo versus TCZ AE rates could be made. The overall AE rate was 479.8 per 100 PY; 84.6% of patients reported at least one AE with the majority being mild or moderate in severity. Infection and infestation AEs were the most frequent AEs (61.2%, 163.7 per 100 PY), followed by musculoskeletal and connective tissue disorder AEs (34.0%, 53.1 per 100 PY) and GI AEs (31.9%, 71.0 per 100 PY). The most common individual AEs were: juvenile arthritis (26.1%, representing flare of the underlying condition), nasopharyngitis (20.7%), headache (13.8%), URTI (10.1%), cough (9.6%), pharyngitis (9.0%), and nausea (8.5%). Among the most common AEs, the proportion of AEs appeared slightly higher (by ~2 - 4.5%) in patients ≥30 kg on TCZ 8 mg/kg than in patients <30kg on TCZ 10 mg/kg, but patient numbers were small in the latter group limiting the conclusions that can be drawn from this comparison.

Infusion-related AEs occurring during TCZ infusion were reported in 11 patients (5.9%, 7.6 per 100 PY), including hypotension and headache (three reports each), and nausea (two reports). All these events were considered mild and resolved without sequelae. A further 33 patients reported at least one AE in the 24 hours post-infusion (23.3 per 100 PY), including dizziness, headache and nausea (four events each), pyrexia and hypotension (three events each), and rash (two events). The majority of these AEs were mild and resolved spontaneously, with two considered severe (viral infection and oropharyngeal pain). There were no anaphylactic or clinically significant hypersensitivity reactions reported during the study.

No deaths were reported but 17 patients experienced 23 SAEs (12.5 per 100 PY), with nine patients reporting serious infections (4.9 per 100 PY, including pneumonia [four events], bronchitis and cellulitis [two events each]). Of these infections, five (4.0 per 100 PY) occurred in patients with a BW ≥ 30 kg on 8 mg/kg TCZ, one (3.7 per 100 PY) in patients with a < 30 kg on 8 mg/kg TCZ, and three (12.2 per 100 PY) in patients with a BW < 30 kg on 10 mg/kg TCZ. While the small number of serious infections precludes meaningful comparison of rates across the treatment groups, given the potential for serious and sometimes fatal infections with TCZ, the result is of interest. There was only one GI SAE (constipation).

There were seven discontinuations due to AEs including arthritis flare, gastroenteritis [patient on placebo], pneumonia [possibly TCZ related], elevated transaminases [serious event, not considered TCZ related], abnormal blood bilirubin [probably TCZ related], and serum sickness [possibly TCZ related]. There were also TCZ dose-interruptions in 24 patients, mostly as a result of infection. Infections leading to dose interruption were again numerically higher in patients with a BW < 30 kg on 10 mg/kg TCZ (21%) compared to patients with a BW < 30 kg on 8 mg/kg TCZ (6%), or patients with a BW ≥ 30 kg on 8 mg/kg TCZ (8%).

Elevations in total cholesterol (34.6%, including 10% with consecutive sustained elevations >170 mg/dL (4.4mmol/l)), LDL cholesterol (11.4%), and/or triglycerides (20%) were observed, but the clinical significance is not known. Neutropaenia was observed in 31% of patients, with seven patients developing Grade 3 or 4 neutropaenia. This occurred more frequently in patients with a BW <30 kg (5/69, 7.2%) than in those ≥ 30 kg (2/119, 1.7%). Grade 1 thrombocytopaenia was observed in 13 (6.9%) of patients.

Elevations in ALT or AST ≥3 x ULN occurred in 3.7% and <1% of patients, respectively.

Of the 185 patients tested for anti-TCZ antibodies, 20 (10.8%) patients had a positive baseline screening anti-TCZ result, and three (1.6%) subjects developed newly positive screening anti-TCZ results post-baseline.

One additional subject had a positive confirmation test, as well as neutralising anti-TCZ antibodies detected at Week 20.

Screening for tuberculosis (TB) was a baseline screening requirement and was repeated at Week 52. Nine patients were positive at baseline and received prophylactic treatment. All five of the patients who had reached their 52 week assessment remained positive, and a further six patients became positive during the trial.

The major safety findings for the entire study (Part I to Part III, through Week 104) are consistent with previously reported safety findings in the Week 40 CSR, including:

- overall AE rates (406.5 per 100 PY)
- infection and infestation AEs (151.4 per 100 PY)
- infusion related AEs within 24 hours of TCZ infusion (16.3 per 100 PY)
- rate of SAEs (11.1 per 100 PY)
- infection and infestation SAEs (5.2 per 100 PY)
- Changes in laboratory parameters (neutrophils, platelets and LFTs)
- No patients had elevations in liver enzymes or hepatic events indicative of Hy's law
- Similar proportion of subjects having consecutive sustained elevations in lipid parameters

Studies MRA318JP and MRA319JP

In the combined studies a total of 142 AEs were reported by 19 patients with most being of mild severity.

The most common individual AEs were: nasopharyngitis (78.9%), pharyngitis (42.1%), gastroenteritis, URTI and arthropod sting (31.6% each); seasonal allergy and eczema (21.1%); bronchitis, impetigo, influenza, allergic conjunctivitis, abdominal pain, diarrhoea, stomatitis and urticaria (15.8% each); and pneumonia, headache, rhinitis, and constipation (10.5% each).

No deaths were reported, but four patients experienced six SAEs, including gastroenteritis (two patients), pneumonia, influenza, myasthenia gravis and sensory disturbance (one patient each). Two patients were withdrawn (myasthenia gravis and development of anti-TCZ antibodies). Two infusion-related AEs were reported, both mild and not requiring discontinuation from TCZ therapy. Total cholesterol and HDL cholesterol levels increased within the normal range up to Week 24 in Studies MRA318JP and MRA319JP, and remained stable thereafter. Mean neutrophil and platelet count decreased by 30% from baseline at Week 24. One patient (5.3%) developed neutralising anti-TCZ antibodies before receiving their fourth infusion of TCZ, and also became positive for IgE antibodies after their fifth TCZ infusion. They had no clinical sequelae, but were withdrawn from the study.

Post-marketing data

Study ML21939 is a Japanese post-marketing surveillance study of pJIA patients treated with TCZ. At the data cut-off date of 3 August 2010, 179 patients were enrolled. The median duration of treatment follow-up was six months, with a total exposure of 93.63 PY. The average age of patients was 15.3 years (range: 2-41 years), mean disease duration 6.8

years (range: 0.2-28.3 years), and 83% were female. There was frequent concomitant use of CS (78%) and conventional DMARDs (82%), with MTX being the most common DMARD (76.5%). Prior biologic DMARD use was reported in 31% of cases.

The overall incidence of AEs was 39.1% (event rate of 149.39 per 100 PY [138 events]). Infection was the most common AE (event rate 52.33 per 100 PY, 49 events in 35 patients), with six patients reporting eight serious infections. Infusion-related AEs occurred in 2.8% of patients, all were mild and no anaphylactic reactions were reported. Lipid abnormalities, abnormal liver function tests, decreases in white blood cells and platelets were reported in 1-5% of patients, but none were considered serious. The incidence of SAEs was 7.3% (event rate of 19.2 per 100 PY [18 events]), including one case of gastric ulcer perforation (complicated by NSAID use). No deaths were reported.

The sponsor's global drug safety data base was checked for all serious cases in the indication of juvenile arthritis with a data cut-off date of 17 December, 2011. A total of 259 SAEs were reported in 128 patients, however only one of these reports (urticaria) was for the treatment indication of pJIA, with the remainder being for the sJIA indication, or unknown/unspecified. Three deaths were reported (acute respiratory distress syndrome with multi-organ failure; pseudomonas infection, sepsis and interstitial lung disease; and cardiac failure, vasculitis, respiratory failure and hepatic failure).

Clinical evaluator's recommendation

The clinical evaluator recommends approval of the sponsor's proposed new indication.

Risk management plan

The TGA OPR has accepted the TCZ-EU-RMP Version 13.0, dated May 2012, plus the Australian specific Annex (Version: 1.0, dated 7 August 2012) for TCZ and recommended further changes (refer to Pharmacovigilance findings).

The Delegate requested the sponsor address these matters in their response to the Delegate's request for further information and follow up where appropriate with the OPR.

Risk-benefit analysis

Delegate considerations

Efficacy

TCZ has demonstrated superiority to placebo in the pivotal phase III study in patients with pJIA. The rate of JIA ACR30 flare at Week 40 relative to Week 16 was 25.6% in TCZ-treated patients compared to 48.1% in placebo subjects (adjusted difference in proportions -21%, 95% CI: -35%, -8%). Patients on baseline MTX or who were DMARD naive obtained the most benefit (rate of flare 19% and 16%, respectively). Patients on TCZ also demonstrated a significantly higher JIA ACR30/50/70 response at Week 40 compared with placebo-treated patients, and reported significant improvements in number of active joints, physician's global assessments VAS, and Pain VAS. Maintenance of efficacy through Week 104 was demonstrated for each of the JIA ACR30/50/70/90 response rates in the OLE, and was similar for the continuous TCZ-treated subgroup and the placebo-treated subjects who had re-initiation of TCZ. The results of the Japanese study MRA318JP/ MRA319JP were supportive, with TCZ-treated patients achieving a 94.7% JIA ACR30 response at Week 12 which was largely maintained throughout the 168 weeks of follow-up.

Safety

The safety profile of TCZ in pJIA appears similar to the safety profile observed in the sJIA population of the same age (2 to 17 years) and in the adult RA population, with no new safety signals identified. Median exposure in the Cherish Study was acceptable at 48 weeks (184.4 PY of exposure), which was extended to 1.85 years after the inclusion of the final Part III data. As previously observed with TCZ, the most frequent AEs to Week 40 were related to infection (163.7 per 100 PY), with nine infections reported as SAEs (4.9 per 100 PY). Infusion-related reactions were reported in 11 patients (5.9%, 7.6 per 100 PY), but all these events were considered mild and resolved without sequelae. There were no anaphylactic reactions during the study. One patient developed anti-TCZ antibodies. Laboratory abnormalities (decreases in neutrophils and platelets, increases in ALT or AST, elevations in cholesterol, LDL cholesterol, and/or triglycerides) were generally mild, not associated with clinical sequelae, and appear consistent with those seen in patients with sJIA. No additional safety concerns were identified during Part III of the Cherish Study. The safety findings of Study MRA318JP/MRA319JP were consistent with the Cherish Study. No deaths were reported in the studies, but three deaths were identified in post-marketing surveillance (not pJIA indication), with infection contributing to at least two of these cases.

Indications

The sponsor agreed with the clinical evaluator to modify the indication based on the baseline disease activity of moderate to severe grading; therefore the indication should be amended to reflect this population.

Data deficiencies

There are limited long-term (multi-year) data which may be important for issues such as malignancy and cardiovascular disease (of note, none of these events were identified in the median 1.85 years of follow-up in Cherish Study). This is currently being addressed by the conduct of a long-term safety study of TCZ in paediatric pJIA patients, and provision of this report will be made a condition of registration. In addition, it doesn't appear that analyses were performed with and without the six Spanish subjects who were protocol violations because the joint assessments were not performed in a blinded, independent manner as required by the protocol. It is not known if this would affect the results.

Summary

Overall at present the submission appears approvable with demonstrated efficacy and an acceptable safety profile.

Proposed action

The Delegate was inclined to approve this submission by Roche Products Pty Ltd to register Actemra (TCZ) for the new indication of treatment of pJIA in patients 2 years of age and older based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit Analysis:

> *Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or in combination with MTX*

In its response to the Delegate's overview, the sponsor was requested to address the following issues:

1. The outstanding matters raised by the RMP evaluator, as detailed above in the RMP section of this document.

2. Protocol violations – it is unclear how the joint assessment data for the affected 19 of 67 study visits for the six Spanish subjects was handled in the analyses, and whether this could have affected the results. Confirm whether analyses were conducted with and without the affected data, and what impact this had on the relevant results.
3. Why was the adverse event profile for patients on placebo during the Part II treatment withdrawal phase of the Cherish Study not presented?

Proposed conditions of registration

The Delegate proposed the following as conditions of registration:

1. The implementation in Australia of the TCZ EU-RMP Version 13.0, dated May 2012, plus the Australian specific Annex (Version: 1.0, dated 7 August 2012), and the responses to the outstanding RMP matters in the sponsor's Pre-ACPM Response of 1 August 2013, included with submission PM-2012-01905-3-3, and any subsequent revisions, as agreed with the TGA.
2. That administration of TCZ for the paediatric indication of pJIA 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 may revisit this condition of registration in the future based upon accumulated safety data from the paediatric population.
3. The provision of the study report on the long-term safety study of TCZ in paediatric patients with pJIA evaluating the risk of malignancies, serious infections, GI perforation, and effects on growth. This study was a post-marketing requirement outlined in the FDA approval letter for the pJIA indication dated 29 April 2013.

Request for ACPM advice

1. In view of the special requirements of children, particularly with regard to IV resuscitation fluids if needed, is the ACPM of the opinion that children with pJIA should only be administered TCZ in a hospital setting (as is the current situation for sJIA), and further that this should be made a specific condition of registration?
2. In view of the lipid abnormalities observed in patients treated with TCZ, the Actemra PI recommends assessment of lipid parameters four to eight weeks after initiation of therapy, and states that "*Patients should be managed according to local clinical guidelines for management of hyperlipidaemia".* Is this recommendation sufficient, or should lipid monitoring be recommended?
3. Should the indication be restricted to patients who have had an inadequate response to or intolerance to MTX, as per the pivotal study inclusion criteria?

Response from sponsor

The sponsor concurs with the Delegate's recommendation to approve Actemra (TCZ) 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL injection vials for the indication: "*Actemra is indicated for the treatment of moderate to severe active pJIA in patients 2 years of age and older. Actemra can be given alone or in combination with methotrexate (MTX).*"

Sponsor's response to issues raised by the Delegate

1. The outstanding matters raised by the RMP evaluator, as detailed above in the RMP section of this document.

The sponsor provided the assurance that the outstanding matters raised by the RMP evaluator will be addressed when the EU-RMP and the corresponding Australian-specific

Annex are next updated. With regard to the draft protocol for the Pharmachild JIA registry an outline (protocol synopsis) of the Registry Study has been submitted to the EMA. Currently, no contractual commitment has been made to conduct this Registry Study with any specific registry provider (for example, Pharmachild). Pharmachild is one of two potential providers being considered. During the full protocol development stage the registry provider will be confirmed. Following completion of the full protocol, Annex 5 of the EU-RMP will be updated with the relevant details.

2. *Protocol violations - it is unclear how the joint assessment data for the affected 19 of 67 study visits for the six Spanish subjects was handled in the analyses, and whether this could have affected the results. Confirm whether analyses were conducted with and without the affected data, and what impact this had on the relevant results.*

In the reporting of the primary endpoint, the data from the six Spanish patients were included in the analyses of both the ITT and per-protocol (PP) populations. The affected joint assessments at selected visits were expected to have minimal impact on the patients' ACR30 flare status, which was based on two joint components and four other components. However, to assess whether inclusion of these data would have affected the study results, the primary analysis based on the PP population has been re-run, excluding the six Spanish patients. The original PP analysis and updated PP analysis excluding the six Spanish patients are presented below.

The exclusion of the data from six Spanish patients has resulted in a minor reduction in the treatment difference. The difference between placebo and TCZ remains statistically significant (p=0.0145), despite the reduced sample size, therefore the overall conclusions for the primary endpoint of the study are not impacted.

Table 6: Cochran-Mantel-Haenszel Analysis of the Proportion of Patients with JIA ACR30 Flare (Part II – PP Population)

	All Placebo	All TCZ
n	70	73
Flared	31 (44.3%)	18 (24.7%)
[95% CI]	[0.33, 0.56]	[0.15, 0.35]
Weighted difference vs All Placebo		-0.19
[95% CI]		[-0.34, -0.05]
p-value		0.0080

Analysis adjusted for the randomization stratification factors (background use of methotrexate and background use of oral corticosteroids) applied at Week 16.
Source: Output etepcmh03_ja3fw_v1_rx2_pp_p2

Table 7: Cochran-Mantel-Haenszel Analysis of the Proportion of Patients with JIA ACR30 Flare (Part II – PP Population) [6 patients at site #165246 excluded]

	All Placebo	All TCZ
n	66	71
Flared	29 (43.9%)	18 (25.4%)
[95% CI]	[0.32, 0.56]	[0.15, 0.35]
Weighted difference vs All Placebo		-0.18
[95% CI]		[-0.33, -0.04]
p-value		0.0145

Analysis adjusted for the randomization stratification factors (background use of methotrexate and background use of oral corticosteroids) applied at Week 16.
Source: Output etepcmh03_ja3fw_v1_rx2_pp_p2_165246

3. *Why was the AE event profile for patients on placebo during the Part II treatment withdrawal phase of the Cherish Study not presented?*

The Cherish Study Week 40 CSR provided information on the AEs reported during the randomised withdrawal period of the study, including rates of AEs per 100 PY for the placebo group.

Adverse events during randomised withdrawal period only

There were several issues with the interpretation of placebo comparison (Part II) AE data and hence caution should be used when interpreting these data:

- As all patients had been exposed to TCZ treatment at the start of Part II, it was acknowledged that prior TCZ treatment could have influence or attribution to events experienced in the placebo group.
- This was a selective population as it only included patients who had been able to tolerate their Part I dose of TCZ.
- This data only included AEs that started after randomisation to placebo.
- Patients receiving placebo were more likely to have flared and hence there were fewer PYs of data in the placebo treatment group. This was selective missing data as it included patients who had previously experienced a response to TCZ and were sensitive to a relapse after withdrawal of TCZ.
- There were also a low number of PYs of exposure (approximately 60 years).

The rate of AEs per 100 PY in Part II is summarised in Table 8. There was a comparable number of patients with at least one AE for the two treatment groups (irrespective of dose), but greater exposure was observed in the all TCZ group compared to the all placebo group. This resulted in a lower rate of AEs for patients receiving TCZ compared to those on placebo.

Table 8: Rate of AEs per 100 Patient Years (withdrawal phase study Part II, safety population – study Part III)

	All Placebo [TCZ] (N = 81)	All TCZ [TCZ] (N = 82)
Duration in study (years)	27.41	32.33
Total patients with at least 1 AE	60	58
Total number of AEs	141	147
Rate of AEs per 100 patient-years	514.4	454.7

Source: staerate02_otrt_nesc_se2_p2
Part I treatment is indicated in [ ]"

Sponsor's comments on Delegate's request for ACPM advice

1. *"In view of the special requirements of children, particularly with regard to IV resuscitation fluids if needed, is the ACPM of the opinion that children with pJIA should be administered TCZ in a hospital setting (as is the current situation for sJIA), and further that this should be made a specific condition of registration?"*

The sponsor agrees with the Delegate's position that children with pJIA should only be administered Actemra in a hospital setting, as is the current situation for sJIA. The sponsor concurs with the text of the Delegate's proposed specific condition of registration for this matter.

2. *"In view of the lipid abnormalities observed in patients treated with TCZ, the Actemra PI recommends assessment of lipid parameters four to eight weeks after initiation of therapy, and states that "Patients should be managed according to local clinical*

guidelines for management of hyperlipidaemia." Is this recommendation sufficient, or should lipid monitoring be recommended?"

The sponsor proposes to refrain from providing specific recommendations for lipid monitoring measures within the Actemra PI. Alerting prescribers to the possibility that some patients may develop lipid abnormalities is considered sufficient, with the expectation that once such an event is identified by the physician, the necessary clinical guidelines for management of hyperlipidaemia would be followed, including with regards to the frequency of lipid monitoring.

3. *"Should the indication be restricted to patients who have had an inadequate response to or intolerance to MTX, as per the pivotal study inclusion criteria?"*

The sponsor concurs with the Delegate's recommendation to approve the indication proposed above. The sponsor acknowledges the prior MTX status of the patient population enrolled in the pivotal study and so, as requested by the Delegate, the clinical trials and AE sections of the PI have been updated to describe the study population in greater detail.

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:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Actemra concentrated injection containing 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL of TCZ to have an overall positive benefit–risk profile for the indication;

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

The ACPM advised that the sponsor should be asked to provide evidence or a suitable justification that dosing based on BW would be associated with similar efficacy outcomes and safety as the preferred dosing based on BSA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM endorsed the amendments recommended by the delegate and specifically advised on the inclusion of the following:

- A statement in the *Clinical Trial* and *Precautions* sections of the PI and relevant sections of the CMI to reference the very small number of patients less than 4 years of age participated in the trial.
- A statement in the *Dosage and Administration* section of the PI and relevant sections of the CMI to ensure prescribing of TCZ is limited to practitioners who are experienced in the management of JIA.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI advising that available data support the use of TCZ only as a second line agent for treatment of pJIA in children aged 2 years and older.
- A statement in the *Precautions* sections of the PI and relevant sections of the CMI to ensure lipid monitoring is performed at regular intervals (3 monthly) during treatment with Actemra.

- A statement in the relevant sections of the PI that makes it clear that while the short term efficacy of TCZ has been demonstrated, TCZ has not been shown to have a safety profile similar to other biological DMARDs approved for use in children with pJIA.

Proposed conditions of registration:

The ACPM endorsed the conditions of registration proposed by the delegate and specifically advised on the inclusion of the following:

- The administration of Actemra for the paediatric indication of pJIA should take place in hospital settings with full resuscitation facilities and immediate access to appropriate medical personnel to deal with anaphylaxis.
- The satisfactory negotiation of the RMP most recently approved by the TGA.
- Negotiation of PI and CMI to the satisfaction of the TGA.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidenced of efficacy and safety provided would support the safe and effective use of these products

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Actemra containing tocilizumab (rch) for the new indication:

Polyarticular Juvenile Idiopathic Arthritis

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

The **full indications** are now:

Rheumtoid 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.

Polyarticular Juvenile Idiopathic Arthritis:

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

Systemic Juvenile Idiopathic Arthritis:

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

Specific conditions applying to these therapeutic goods

- The Actemra (TCZ (rch)) EU-Risk Management Plan (EU-RMP), Version 13.0, dated May 2012, plus an Australian Specific Annex (ASA) Version 1.0, dated 7 August 2012, and the responses to the outstanding RMP matters in the sponsor's Pre-ACPM Response of 1 August 2013 included with submission PM-2012-01905-3-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The administration of TCZ for the paediatric indication of pJIA should only take place in a hospital setting with immediate access to appropriate medical personnel and with full resuscitation facilities to manage anaphylaxis.
- The following study must be submitted to the TGA for evaluation, as soon as possible after completion:
  - The study report on the long-term safety study of TCZ in paediatric patients with pJIA evaluating the risk of malignancies, serious infections, GI perforation, and effects on growth. This study was a post-marketing requirement outlined in the FDA approval letter for the pJIA indication dated 29 April 2013.

Attachment 1: Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2: Extract from the Clinical Evaluation Report

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