Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for tocilizumab (rch)

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

September 2016

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 <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACR	American College of Rheumatology
AE	Adverse Event
AI	Autoinjector
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve (drug concentration-time curve)
AUC_{0-t}	Area under the curve from time 0 to trough
AUC_{inf}	Area under the curve from time 0 to infinity
AUC_{last}	Area under the curve from time 0 to last observation
BREVACTA	Study NA25220
CDS	Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicine Information
C_{max}	Maximum concentration
CrCL	Creatinine clearance
CRP	C-reactive protein
CSR	Clinical Study Report
C_{trough}	Trough plasma concentrations
DAS28	Disease Activity Score in 28 Joints
DB	Double Blind
DMARD	Disease Modifying Anti-Rheumatic Drug
EMA	The European Agency for the Evaluation of Medicinal Products
E_{max}	Maximum effect

Abbreviation	Meaning
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HAQ-DI	Health assessment questionnaire disability index
HDL	High-density lipoprotein
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
ITT	Intention-to-treat
IV	Intravenous
JIA	Juvenile idiopathic arthritis
k_a	Absorption rate constant
LDL	Low-density lipoprotein
LFT	Liver function test
LTE	Long term extension
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MAS	Macrophage Activation Syndrome
MI	Myocardial infarction
mIL-6R	Membrane-bound interleukin-6 receptor
MRA	Myeloma receptor antibody (tocilizumab)
mTSS	modification of the Sharp score
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open Label Extension
PBRER	Periodic Benefit-Risk Evaluation Report

Abbreviation	Meaning
PD	Pharmacodynamics
PFS	Pre-filled syringe
PI	Product Information
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMS	Post-Marketing Surveillance
PP	Per protocol
PSUR	Periodic Safety Update Report
PtGADA	Patient's Global Assessment of Disease Activity
PY	Patient-years
QoL	Quality of Life
RA	Rheumatoid arthritis
RO4877533	Tocilizumab
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SC	Subcutaneous
sIL-6R	Soluble interleukin-6 receptor
SIR	Standardised incidence rates
SJC	Swollen joint count
sJIA	Systemic onset juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics
SUMMACTA	Study WA22762
TCZ	Tocilizumab
TEAE	Treatment emergent adverse event

Abbreviation	Meaning
TJC	Tender joint count
TNF	Tumour necrosis factor
t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
VAS	Visual analogue scale

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new dosage form, new dose, new strength and new route of administration)
Decision:	Approved
Date of decision:	19 January 2016
Date of entry onto ARTG	21 January 2016
Active ingredient:	Tocilizumab (rch)
Product name:	Actemra SC
Sponsor's name and address:	Roche Products Pty Limited 4-10 Inman Road Dee Why NSW 2099
Dose form:	Solution for injection; Single use pre-filled syringe
Strength:	162 mg/0.9 mL
Container:	Pre-filled syringe
Pack size:	1 syringe; 4 syringe pack
Approved therapeutic use:	*Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs.* *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX.* *In the two groups of patients above, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.* *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.*
Route of administration:	Subcutaneous (SC) injection
Dosage:	162 mg (one pre-filled syringe) given once every week
ARTG number:	234034

Product background

Tocilizumab (TCZ) is a recombinant humanised monoclonal antibody of the immunoglobulin IgG1.

TCZ binds specifically to both soluble and membrane-bound interleukin 6 (IL-6) receptors and has been shown to inhibit soluble and membrane bound IL-6 receptor (sIL-6R- and mIL-6R) mediated signalling. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including rheumatoid arthritis. In clinical studies with TCZ, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed.

At the time of submission, TCZ was already approved for the following indications via intravenous (IV) route of administration:

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.*
>
> *ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see CLINICAL TRIALS) in combination with MTX in those not previously treated with MTX.*
>
> *In the two groups of patients above, ACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*
>
> *ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.*

Polyarticular juvenile idiopathic arthritis:

> *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). Tocilizumab can be given alone or in combination with MTX.*

Systemic juvenile idiopathic arthritis:

> *The treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Tocilizumab can be given alone or in combination with methotrexate (MTX).*

DMARD(s), Disease Modifying Anti-Rheumatic Drug(s). Clinical grouping of unrelated drugs shown to slow disease progression by targeting mechanisms of pathogenesis in contrast with NSAIDs (non-steroidal anti-inflammatory drugs) such as ibuprofen that treat inflammation symptomatically but not underlying cause) or corticosteroids that reduce the immune response temporarily but not enough to halt long term disease progression.

This submission is for registration of a subcutaneous (SC) route of administration for the treatment of rheumatoid arthritis only and does not include approval or application for registration for pJIA (polyarticular juvenile idiopathic arthritis) or sJIA (systemic juvenile idiopathic arthritis) indications via the SC route. The following table (Table 1) summarises the currently registered dosage forms and strengths of Actemra.

Table 1. Currently registered dosage forms and strengths of Actmera

AUST R	Strength	Dosage Form
149403	80 mg	Single use vial containing 80 mg of Actemra in 4 mL (20 mg/mL). Packs of 1 and 4* vials.
149404	200 mg	Single use vial containing 200 mg of Actemra in 10 mL (20 mg/mL). Packs of 1 and 4* vials.
149402	400 mg	Single use vial containing 400 mg of Actemra in 20 mL (20 mg/mL). Packs of 1 and 4* vials.

*The packs of 4 vials are not marketed.

This formulation was originally submitted in another application.

The submission proposes registration of the following dosage form and strength as shown in Table 2 below.

Table 2. Proposed registration of new route, dosage form and strength

Submission application	Strength	Dosage Form
PM-2014-04309-1-3	162 mg	Single use pre-filled syringe with needle safety device containing 162 mg of Actemra in 0.9 mL (180 mg/mL). Packs of 4 syringes.

Regulatory status

The product received initial registration for IV administration on the Australian Register of Therapeutic Goods (ARTG) in May 2009. ARTG registration was extended to SC injection indicated for the treatment of rheumatoid arthritis on 21 January 2016.

At the time the TGA considered this application, a similar application had been approved in the European Union (April 2014), Japan (March 2013), USA (October 2013), Canada (May 2014) and New Zealand (April 2015). In addition to those major reference regions, TCZ for SC administration had been approved in: Argentina, Aruba, Belarus, Bosnia and Herzegovina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Georgia, Guatemala, Hong Kong, Israel, Jamaica, Kuwait, Lebanon, Macau, Macedonia, Mexico, Mauritius, Montenegro, Myanmar, Paraguay, Philippines, Qatar, Russia, Serbia, South Korea, Taiwan, Ukraine, Uruguay and United Arab Emirates.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Actemra concentrated solution for IV infusion is a clear to opalescent, colourless to pale yellow sterile solution containing TCZ concentrate (20 mg/mL), polysorbate 80, sucrose, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate dihydrate and water for injections.

In its letter of application for this submission, Roche Pty Ltd provided a Reviewer's Guide to assist evaluation by highlighting new or revised information in the dossier compared to the previous SC application.

Drug substance (active ingredient)

TCZ, also named Myeloma Receptor Antibody (MRA) is a recombinant humanised monoclonal antibody that selectively binds to human IL-6R receptor. It is an IgG1κ (gamma 1, kappa) antibody with a typical H2L2 structure. TCZ is composed of two heterodimers, each of which consists of a heavy and a light polypeptide chain. The light chain contains of 214 amino acids and the heavy chain 448 amino acids. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. TCZ binds to both sIL-6R and mIL-6R.

The molecular formula and theoretical molecular weight of the TCZ antibody (applicable to the polypeptide moiety only) are as follows:

- Molecular formula: $C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$
- Molecular weight: 144,985 Da

The structure of the drug substance remains unchanged from the approved IV formulation.

Drug product

Formulation

Actemra SC is supplied as a sterile, colourless to slightly yellowish, preservative free liquid solution in a single use 1 mL prefilled syringe (PFS) with a staked in 27G ½ in hypodermic needle which is sealed with a rigid needle shield (RNS) and assembled with a needle safety device (NSD), delivering 162 mg TCZ in a 0.9 mL solution. Actemra SC also contains histidine, histidine hydrochloride, polysorbate 80, arginine, arginine hydrochloride, methionine and water for injections.

Quality summary and conclusions

As this submission is a re-submission of the previous application, evaluation reports for the previous application were also applicable and the unchanged aspects in the current submission have not been re-evaluated.

Batch release conditions of registration for delegate

Batch release testing is *not required* as the active substance is unchanged and its stability in the new formulation has been established in stability studies. Monitoring of product quality will be conducted through the post-market surveillance program.

However inclusion of the following wording in the conditions of registration is recommended:

> It is a condition of registration that as a minimum, the first five independent batches of:
>
> ACTEMRA tocilizumab (rch) 162 mg/0.9mL solution for injection pre-filled syringe
>
> (Prov AUST R234034)
>
> Imported into/manufactured in Australia are not released for sale until the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
>
> The sponsor must supply:
>
> 1. Certificates of Analysis of all active ingredients (drug substance) and final product.
> 2. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included)
> 3. Evidence of maintenance of registered storage conditions during transport to Australia
> 4. A single container from the first batch to be released in Australia for label compliance assessment.

Data should be submitted before release of each batch and with sufficient lead time to allow for review.

This protocol release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

III. Nonclinical findings

The nonclinical evaluation of TCZ via the SC route was based two studies on analytical methods submitted with the previous registration submission, one SC bioavailability study in minipigs and a 9 week SC toxicity study in cynomolgus monkeys. As the drug substance and route of administration remains unchanged, the findings remain valid for this resubmission.

Pharmacokinetics

The single dose pharmacokinetics study in minipigs compared IV and SC administration of around 20 mg/kg whereas the toxicity study in cynomolgus monkeys involved repeat dosing via SC administration of 100 mg/kg/week for 9 weeks.

Comparison between the SC and IV routes in the single dose study in minipigs showed that exposure, as assessed by the area under the concentration versus time curve (AUC) values, was slightly lower for the SC route (area under the curve Day 0 to Day 28 ($AUC_{0\text{-}28d}$) 57.8 versus 68.6 mg x h/mL for the SC and IV routes, respectively). As expected for the SC route, peak plasma concentration (C_{max}) (190 versus 495 µg/mL) was lower and the time to C_{max} (t_{max}) was longer (48 h versus 0.08 h). Plasma half-life was longer for both the routes (around 11 and 12 days for the SC and IV routes, respectively). Absorption after the SC route was 83.5%.

Comparison of the currently used IV dose regimen (8 mg/kg every 4 weeks) versus the intended SC regimen (162 mg SC weekly; or approximately 3.24 mg/kg/weekly for a

person weighing 50 kg) in humans showed slightly lower $AUC_{0\text{-}4week}$ (IV versus SC: 39.5 versus 33.0 mg x h/mL; historical value for the IV route: 35.0 mg x h/mL) and mean plasma concentration (C_{mean}) values (58.7 versus 49.1 µg/mL; historical value for the IV route: 52.1 µg/mL) for the SC regimen. As in minipigs, absorption after SC administration of TCZ in humans was around 80% (contrasted with 70% observed in cynomolgus monkeys in the previously submitted study; ADM04-0014).

Similar to humans, pharmacokinetic data from a 9 week repeat-dose toxicity study in cynomolgus monkeys showed that accumulation was seen following repeated administration with a Day 1 to Day 50 ratio of approximately 3 for both AUC and C_{max}. The area under the curve from first dose to 7 days ($AUC_{0\text{-}7d}$) values in the monkey study were 151 and 478 mg.h/mL (calculated to be 604 and 1912 mg.h/mL for four weeks) on Days 1 and 50, respectively, which are 18 to 58 times the human exposure (area under the curve from dosing to 4 weeks ($AUC_{0\text{-}4\ wk}$): 33 mg.h/mL). Hence, it is considered that sufficient exposure was attained in the repeat dose toxicity study in monkeys.

Toxicology

A 9 week repeat-dose toxicity study has been submitted in monkeys using the SC route of administration. The cynomolgus monkey was shown in a previous evaluation report on TCZ to be an appropriate model for toxicity testing because it showed adequate specific cross reactivity with TCZ in a panel of normal tissues in tissue binding studies, and displayed similar pharmacological responsiveness to key markers of RA. Moreover, human and cynomolgus monkey IL-6R were shown to share 97.3% sequence homology at the amino acid level.

While the repeat dose toxicity study in monkeys was conducted according to Good Laboratory Practice (GLP) it had only one treatment group and hence a dose-response could not be assessed. However, this is not considered a major deficiency since repeated dose toxicity studies (up to 6 months duration) have previously established the dose-dependence of toxicity via the IV route. The relative exposure based on AUC ratio was up to 59 (compared to human exposure) in a 26 week IV study in cynomolgus monkeys.

In the SC repeat-dose toxicity study (100 mg/kg/week SC TCZ) submitted in the current submission, no significant toxicity was seen at relative exposure of above 18 fold. Although a few changes were noted in organ weights or histology (testes, thymus, ovaries and kidneys) these were not correlated with histological changes, or the histological changes occurred in only one animal/group, and were reported to be within background incidence. Similarly, a few changes in haematology were considered incidental. Overall, the changes are not considered treatment-related.

In previously submitted IV toxicity studies in cynomolgus monkeys, toxicity was mainly restricted to the haematopoietic, humoral and cellular immune systems. Significant changes occurred at doses considerably higher than those in humans at the recommended clinical dose (IV). These findings were considered to be associated with the pharmacologic activity of TCZ, that is, through inhibition of the IL-6R signalling pathway. However, these findings were accompanied by only a few TCZ related effects on the morphology of either primary or secondary organs of the immune system, and did not translate to generally increased rates of infection. In these IV toxicity studies, changes in haematopoietic system in cynomolgus monkeys occurred only when TCZ was given daily but not when administered weekly. The absence of effects on haematology in the current SC study could be related to the dosing interval (weekly).

Overall, there was little evidence of toxicity of TCZ following weekly treatment with a SC dose of 100 mg/kg for 9 weeks.

Local tolerance and immunogenicity

A separate study on local tolerance was not submitted. However, local reactions and histological changes at the injection site were monitored in the 9 week repeat-dose toxicity study in cynomolgus monkeys (100 mg/kg/week SC TCZ). The intended clinical formulation (Actemra containing 180 mg/mL TCZ) was used in this study which did not show any treatment related effects at the injection site.

The local SC or peri-venous SC tolerability was previously investigated in rabbits but the concentrations of TCZ tested were < 100 mg/mL and hence these studies were not considered relevant to the current application (as the intended concentration of TCZ is 180 mg/mL).

The sponsor has not submitted a separate study to address skin sensitisation potential of TCZ. A skin sensitisation study in guinea pigs is not possible because TCZ (1 and 10 mg/kg) has been previously shown to cause severe active systemic anaphylaxis (ASA) reactions in guinea pigs when TCZ was administered with and without Freund's complete adjuvant (FCA) in antigenicity studies in this species. However, there was no evidence of immunotoxicity in mice, suggesting that the ASA reaction is species specific. In mice, testing used intra peritoneal administration of either the vehicle or 10 μg TCZ or OVA (each; OVA = ovalbumin) or (without aluminium hydroxide gel) 10 μg TCZ IV (presumably two weekly doses, with aluminium hydroxide gel). This was followed by a 72 h passive cutaneous anaphylaxis (PCA) reaction (using 5 mg IV TCZ or OVA) test in rats administered sera from treated mice (cutaneously). No ASA or PCA reactions were seen to arise from TCZ or vehicle sensitised sera from mice.

The draft PI (as well as the currently approved PI) lists hypersensitivity reactions, including anaphylaxis in the subsection, 'Precautions'. Moreover the PI recommends permanent discontinuation of the product in the event of an anaphylactic reaction or other serious hypersensitivity reaction.

Based on the above, data on local tolerance and immunogenicity are considered adequate.

Excipients

There are no issues related to the presence of excipients in the intended product. All the excipients in the formulation have been used in other injectable products.

Paediatric use

The SC product is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- Bioavailability of TCZ following a single SC dose of around 20 mg/kg in minipigs was 83.5%, a level similar to that observed in humans via the SC route.
- In the repeat-dose study in monkeys, injection site reactions after SC administration of the clinical formulation were unremarkable.
- As the anticipated systemic exposure of TCZ with the clinical dose of the SC formulation was lower than the exposure with the current IV dose regimen, there are no additional toxicological concerns with the proposed SC dosage regimen.
- There are no issues of concern with the excipients used in the new formulation as all of them are currently used in other registered injectable products.

- Based on the nonclinical data provided for Actemra (SC) and the bridging data evaluated in this report, there are no nonclinical objections to the registration of Actemra TCZ solution for subcutaneous injection.
- The nonclinical evaluator also recommended changes to the draft PI but these are beyond the scope of this AusPAR.

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.

Introduction

Clinical rationale

The sponsor proposed that the registration of a SC formulation, in addition to the IV formulation, will have several benefits:

- Improved patient convenience and preference (IV or SC)
- Shorter administration time
- No requirement for intravenous access
- The option for patients to receive Actemra at home
- An alternative route of administration for patients with poor venous access
- Lower resource utilisation when administered at home.

Contents of the clinical dossier

The submission contained the following clinical information:

- 4 Phase I studies in healthy subjects:
  - WP18097
  - BP22065
  - NP25539
  - BP21894)
- 2 studies in patients with RA:
  - NP22623 (a Phase Ib study)
  - MRA227JP (a Phase I/II dose escalation study in Japanese patients)
- 3 population PK reports
- 3 Phase III studies, randomised, double-blinded in patients with RA investigating SC Actemra
  - WA22762
    - Primary report, open label extension, immunogenicity report
    - Open label extension to Week 97*
  - NA25220

    - § Primary report
    - § Open label extension to Week 96*
  - MRA229JP in Japanese patients is considered a supportive study
    - § Open label extension to Week 108 (synopsis only; full clinical study report (CSR) available only in Japanese)*
  - WA18696
    - § Open label extension (not related to SC administration of TCZ)*
- Drug Safety Report*
- Research Report (Anaphylaxis based on Health Claims Data)*
- 2 Periodic Benefit-Risk Evaluation Reports (PBRERs)*
- Summary of Clinical Safety
- Literature references.

*Denotes either new data or further data was included (primarily extension of previous studies) compared with previous submission.

Paediatric data

Although TCZ via the IV route is indicated for polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis, the submission did not involve proposing authorisation for TCZ via the SC route for these indications therefore no paediatric data was submitted.

Good clinical practice

All the clinical studies presented in the submission are stated to have been conducted according to Good Clinical Practice (GCP) guidance.

In Study WA18696 (submitted as a condition of registration), critical findings of non-compliance were observed at 3 sites that may have impacted patient safety and/or data integrity. The sponsor implemented corrective and preventative actions and deemed that:

> *The validity and integrity of the analyses were not affected at any of the above 3 sites, and including all available data in the analyses is a conservative approach, as it ensures reporting of the study in its entirety*.

Pharmacokinetics

Studies providing pharmacokinetic data

Extended duration data from Studies WA22762 and NA25220 were submitted (along with data available from the previous submission). These studies of extended duration were deemed pivotal and satisfactory for PK evaluation.

Evaluator's conclusions on pharmacokinetics

The following is a summary of the PK from the previous evaluation (initial submission):

- Absolute bioavailability from SC route was 77% (clearance changing with concentration) (Protocol: WP18097)

- Absorption was slower by the SC route with a median t_{max} of 48 hours compared to 2 hours by IV route. Absorption half-life was about 4 days
- Both SC presentations (pre-filled syringe and autoinjector) had similar plasma concentration profiles but with high inter-subject variability. Bioequivalence between them was seen for area under the curve (AUC) from 0 (dosing) to infinity (AUC_{inf}) but was slightly bioinequivalent for the area under the curve from dosing to last measurable point (AUC_{last}) (0.90-1.27) and C_{max} (0.94-1.27)
- Weight had a significant effect on clearance and volume of distribution. In simulations from the population PK analysis, clearance was decreased by 25% in a 40 kg person and increased by 43% in a 140kg person
- Thigh administration increased bioavailability by 10%.

The evaluator of this resubmission had the following conclusions:

- PK from the WA22762 open label extension (OLE) study is consistent with the double blind (DB) phase of the study with higher pre-dose TCZ plasma concentrations following 162 mg SC weekly administration compared with 8 mg IV every 4 weeks administration.
- PK from the NA25220 OLE is consistent with the double blind (DB) phase of the study, with both the PFS and AI (autoinjector) SC presentations resulting in similar pre-dose TCZ concentrations.

Pharmacodynamics

Studies providing pharmacodynamic data

Studies WA22762 and NA25220 were used in analysis of pharmacodynamics (PD).

Evaluator's conclusions on pharmacodynamics

The following is a summary of the PD data from the previous evaluation:

- PD outcomes were similar from SC and IV routes
- A dose-finding study indicated similar effects on ACR20, 50 and 70 responses and CRP from once weekly and once fortnightly dosing but a better DAS28 response for once weekly although this was not statistically significant.[1,2]

In addition, the evaluator of this resubmission added the following conclusions:

- PD from the WA22762 OLE Study is consistent with the PD from the DB phase of the study:
  - Mean sIL-6R levels were maintained and comparable in the SC and IV arms
  - Mean CRP levels were maintained in the normal range for the SC and IV arms
  - Mean ESR levels remained low for the SC and IV arms.

[1] ACRχ; American College of Rheumatology Criteria Response: A measurement, recording improvement in disease state of rheumatoid arthritis, with χ = corresponding with a global improvement of at least that number (as a percentage).
[2] DAS28; Disease Activity Score 28-Erythrocyte Sedimentation Rate: Combined index to measure rheumatoid arthritis disease activity using swollen/tender joint number and other disease factors. van der Heijde et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990 Nov; 49(11): 916-920.

- PD from the NA25220 OLE Study is consistent with the PD from the DB phase of the study:
  - Mean sIL-6R, CRP and ESR levels were maintained longer term
  - Mean sIL-6R, CRP and ESR levels were comparable in the PFS and AI SC arms.

Dosage selection for the pivotal studies

SC dose selection for the pivotal studies was based on four clinical pharmacology studies investigating PK and PD in healthy subjects and PK, PD, efficacy and safety of TCZ following SC administration in RA patients. The PD profiles (CRP, ESR, and sIL-6R) of the SC TCZ 162 mg weekly regimen were determined to be most comparable to the TCZ IV 8 mg/kg dosing regimen. The 162 mg SC every two weekly dose regimen produced a slower and less pronounced PD response. In the current submission, the sponsor stated that:

> *Study NA25220 has been established as a suitable lower dosing regimen, as part of dose modification for laboratory abnormalities*.

Efficacy

Studies providing efficacy data

Study WA22762 and Study NA25220 were submitted and considered pivotal studies in evaluating the efficacy of SC TCZ.

In addition, Study MRA229JP, Study ML28338 and Study WA18696 were considered supplementary studies in efficacy evaluation.

Evaluator's conclusions on efficacy

Results from the open label extensions of the pivotal WA22762 and supportive MRA229JP studies showed that the comparable efficacy demonstrated for weekly (WA22762) or 2 weekly (MRA229JP) SC and 4 weekly IV TCZ during the DB phase of the studies (based on ACR 20/50/70, DAS28 and so on) was maintained for up to 2 years in patients remaining on SC TCZ or IV TCZ for the total duration of the study and for those switching from IV to SC or SC to IV TCZ. Patients weighing ≥ 100 kg were noted to have a lower response for ACR20 on SC TCZ but a higher response for ACR50 and ACR70, compared to IV dosing at Week 24. At Week 97, patients weighing ≥ 100 kg again had lower response rates compared with lighter patients, with the IV group having lower response rates than the SC group in the ≥ 100 kg group. Patient numbers in the ≥ 100 kg switch groups were too small for reliable interpretation.

In the pivotal NA25220 study, patients who commenced and remained on 2 weekly SC TCZ had no reduction in efficacy during the up to 96 weeks of follow up. Patients switching from placebo to SC TCZ at Week 24 responded rapidly, reaching comparable levels to those on continuous TCZ after approximately 8 weeks of treatment, and maintaining this response for the duration of the study. At Week 96, patients weighing ≥ 100 kg had lower response rates compared with lighter patients, but the patient numbers were very low (maximum of 7 patients) making interpretation of these results difficult. However the results were consistent with those reported at Week 24 when the patient numbers were higher in the ≥ 100 kg group (26 patients).

Study ML28338 (long term extension (LTE) of US patients completing either WA22762 or NA25220) provided further supportive evidence of the long-term efficacy of SC TCZ.

It is noted that the ACR20/50/70 response rates at Weeks 24, 48/49, and 96/97 were similar for patients receiving SC TCZ weekly in Study WA22762 and SC TCZ twice weekly in Study NA25220. Although these studies were not designed to be directly compared, the patient populations in both studies were similar (moderate to severe RA with an inadequate response to DMARDS).[3] The dosage selection for the pivotal studies was based on PD profiles, however in view of the similar efficacy responses for the two dosage regimens, the sponsor will be asked to comment on this finding and whether there are any planned or existing studies directly comparing clinical outcomes for the two SC dosing regimens. Whether the dosing model for SC TCZ is appropriate was also raised by the TGA's Advisory Committee on Prescription Medicines (ACPM) following the original submission.

In Study MRA229JP, self-injection was undertaken by 82 patients. No difference in efficacy was noted between the ACR 20/50/70 response rates or DAS28 scores achieved with self-injection versus those achieved when TCZ was administered by a healthcare professional.

Safety

Studies providing safety data

As agreed with the TGA, the sponsor submitted updated data from the SC TCZ clinical trial program beyond that submitted in the previous application (Studies WA22762, NA25220, MRA229JP, and ML28338), post-marketing safety data from regions where SC TCZ has marketing approval and specific analyses on hypersensitivity and anaphylaxis to TCZ to address the concerns of the risks for serious hypersensitivity and/or anaphylactic reactions in the home setting.

The following pivotal studies provided evaluable safety data: Study WA22762 and Study NA25220. Additional safety data was provided in Study MRA229JP (only the synopsis was submitted) and Study ML28338.

There were no pivotal studies that assessed safety as a primary outcome.

Patient exposure

Mean and median exposure in Study WA22762 was longer for SC administration of TCZ than for IV administration (1.38 and 1.72 years versus 1.12 and 1.44 years, respectively). A further mean (median) 1.20 (1.33) years and 1.19 (1.29) years of SC and IV TCZ exposure, respectively, were added from the switch arms during the OL phase of the study.

In Study NA25220, the total patient years (PY) of exposure was 404.3 PY (n = 437 patients) in the TCZ PFS arm, 211.6 PY in the TCZ PFS to Autoinjector (AI) switch arm (n = 168 patients), 75.6 PY in the placebo to TCZ PFS switch arm (n = 61 patients), and 78.7 in the placebo to TCZ AI switch arm (n = 59 patients). This is based on the duration of actually received treatment over the 96 weeks of the study in the TCZ PFS treatment arm, but limited to TCZ exposure during the OL period for the other 3 treatment arms. For escape patients (patients who stopped or escaped randomised treatment assigned to them when the patient fails to meet pre-specified endpoints or suffers a flare/worsening of disease status) exposure to TCZ weekly was 126.5 PY in the prior TCZ arm (n = 98 patients) and 129.3 PY in the prior placebo arm (n = 91 patients).

[3] DMARD(s), Disease Modifying Anti-Rheumatic Drug(s). Clinical grouping of unrelated drugs shown to slow disease progression by targeting mechanisms of pathogenesis compared with NSAIDs (non-steroidal anti-inflammatory drugs) such as ibuprofen that treat inflammation symptomatically but not underlying cause) or corticosteroids that reduce the immune response temporarily but not enough to halt long term disease progression.

Of the other studies, only Study ML28338 gave patient exposure data with a total PY duration of 251.3 PY for the overall population.

Safety issues with the potential for major regulatory impact

Safety of home based therapy

The sponsor has provided long term safety data for patients receiving SC TCZ in clinical trials and post marketing data in support of the safety of home based therapy. However while the data does address the relative safety of SC administration of TCZ versus IV TCZ, for the majority of the data it was not reported whether SC administration occurred in a home setting or a healthcare setting. While the clinical trial protocols all allowed home administration after demonstrated competence in self-administration (or administration by a caregiver) at the clinical site, only the Japanese study (MRA229JP) reported adverse events (AEs) separately for patients before and after the start of self-injection. Similarly for the post-marketing data, safety of SC TCZ (versus IV TCZ) has been presented, but it is not reported separately for clinical site and home based administration (the sponsor will be asked to provide this information). Therefore the decision regarding the safety of home based therapy is being made on the basis of the relative safety of SC versus IV TCZ administration which has occurred primarily in the healthcare setting, not on demonstrated safety of SC TCZ in the home.

Important identified and potential risks

In the Australian specific Risk Management Plan (RMP), the Important Identified Risks are:

- Serious infection
- Complications of diverticulitis (including GI perforation)
- Serious hypersensitivity reactions

The Important Potential Risks are:

- Neutropenia
- Thrombocytopenia
- Elevated hepatic transaminases
- Elevated bilirubin (essentially indirect)
- Immunogenicity
- Elevated lipids
- Malignancies
- Demyelinating disorders
- Viral reactivation
- CYP450 enzyme normalisation

Post-marketing data

Two Periodic Benefit Risk Evaluation Reports (PBRERs) were submitted covering the periods 11 October 2013 to 10 April 2014, and 11 April 2014 to 10 October 2014. Since the international birth date (11 April 2005) to 10 October 2014 the estimated cumulative market exposure to TCZ is 399,041 patients (equivalent to 323,111 PYs) of which 382,166 patients (95.8%) received IV TCZ and 16,875 patients (estimated 13,664 PYs) received SC

TCZ. A further 24,897 patients received TCZ while participating in clinical trials (34,065.1 PYs on IV TCZ and 3,715.7 PYs on SC TCZ).

During the combined periods, the following actions were taken:

- Stevens-Johnson syndrome (SJS) was identified as a new adverse drug reaction resulting in the update of the core data sheet (CDS), SPC, patient information leaflets, and Informed Consent Forms and other relevant clinical trial documents for a number of ongoing studies.
- A drug safety report (DSR) was prepared for autoimmune disorders, but the signal was refuted by the Marketing Authorisation Holder (MAH) following a thorough assessment.
- The SC formulation of TCZ was approved in the European Union for the treatment of moderate to severely active RA in adult patients who have had an inadequate response to one or more DMARDs.

Serious hypersensitivity reactions and anaphylaxis are considered events of interest for TCZ (see Table 4 below). During the period of the PBRERs, no new notable findings related to these events were identified and the safety profile of SC TCZ was found to be comparable with the safety profile of IV TCZ (with the exception of injection site reactions which were more common with SC TCZ).

Table 4: Cumulative rates of serious hypersensitivity reactions (PBRER 11/4/14 to 10/10/14)

	Events per 100 PY (95% CI)	
	IV all exposure population (02 May 2012)	SC all exposure population (4MSU† Data Cut October 2012)
Rates of Serious Hypersensitivity‡	0.27 (0.20, 0.36)	0.37 (0.14, 0.81)
Rates of Anaphylaxis	0.05 (0.02, 0.10)	0 (0.00, 0.23)

†Four-Month Safety Update; ‡Serious hypersensitivity events were defined as all SAEs that occurred during or within 24 hours of a dose and which were not judged 'unrelated' to treatment by the investigator, regardless of whether or not they were consistent with hypersensitivity.

Evaluator's conclusions on safety

- Injection site reactions with the TCZ PFS presentation occurred at a similar rate in both pivotal studies (26.1 (23.0, 29.4) versus 22.01 (17.68, 27.09) events per 100 PY for WA22762 and NA25220, respectively). These rates were comparable to the rate seen with IV administration of TCZ (33.6 (27.1, 41.3) events per 100 PY) in WA22762.
- Hypersensitivity reactions with the TCZ PFS presentation occurred at a similar rate in both pivotal studies (8.8 (7.1, 10.8) versus 5.69 (3.61, 8.54) events per 100 PY for WA22762 and NA25220, respectively), which was lower than the rate seen with IV administration (14.8 (12.3, 17.7)) in WA22762.
- Serious hypersensitivity reactions with the TCZ PFS presentation occurred at a similar rate in both pivotal studies (0.5 (0.2, 1.2) versus 0.00 (0.00, 0.91) events per 100 PY for WA22762 and NA25220, respectively), which was comparable to the rate seen with IV administration (0.2 (0.03, 0.9)) in WA22762.
- To date, only one (non-fatal) anaphylaxis event has been reported with SC TCZ administration. This needs to be put in the context of an estimated 13,664 PYs of post-authorisation exposure to SC TCZ, versus 309,447 PYs of post-authorisation exposure to IV TCZ with an estimated anaphylaxis rate of 0.05 (95% confidence interval (CI): 0.02, 0.10) events per 100 PY based on cumulative market exposure up till 10 October

2014. Based on the adult IV TCZ RA clinical trial program, the incidence proportion of anaphylactic reactions was 0.198%, while the overall adjudicated incidence proportion based on clinical trials in all indications and spontaneous reports was 0.052%.

- Based on a retrospective cohort study of anaphylaxis in multiple cohorts of RA patients treated with commonly used biologics, rates of anaphylaxis following IV administration were similar (overlapping 95% CIs) for TCZ, infliximab and abatacept. Only abatacept had both IV and SC formulations in the database, and anaphylaxis rates were comparable for both formulations.
- Of the 122 adjudicated anaphylaxis events following IV TCZ administration, 91% occurred in association with the first 5 infusions. It is not known whether this would also reflect the distribution of anaphylaxis events following SC administration.
- Development of antibodies is not a good predictor of hypersensitivity, anaphylaxis, or injection site reactions (ISRs).
- When compared to the rates in the 24 week DB and interim OLE reports, the rate of AEs of hypersensitivity declined over the course of the pivotal studies.
- The AE profiles were comparable for the weekly and 2 weekly SC TCZ dosing regimens, and were consistent with the known safety profile of IV TCZ.
- Safety has not specifically been demonstrated for SC TCZ in the home based setting.

No other newly identified safety risks were identified, and post marketing data were considered to be consistent with the safety profile observed in the clinical trial data. Of note, there was no data specifically related to home based use of SC TCZ in these reports.

First round benefit-risk assessment

First round assessment of benefits

The benefits of SC administration of TCZ in the proposed usage are:

- Comparable efficacy (non-inferiority) for SC TCZ 162 mg weekly and the approved IV dosing regimen (8 mg/kg IV 4 weekly) which is maintained for up to 2 years of follow up.
- Provides an alternative to IV dosing which may be preferable to patients with poor venous access.
- Potentially allows for the convenience of home administration in patients for whom this is considered appropriate by their health care professional.
- AE profile that is consistent with that known for the IV dosing regimen.

First round assessment of risks

The risks of SC administration of TCZ in the proposed usage are:

- Comparable rates of injection site reactions, hypersensitivity reactions and anaphylaxis for SC and IV administration of TCZ, however the data for SC use is based on fewer PYs of follow-up (13,664 PYs versus 309,447 PYs, respectively).
- Non-serious hypersensitivity reactions may not be recognised (or reported) by the patient resulting in ongoing use of TCZ rather than permanent discontinuation of treatment. A subsequent, more serious reaction could then occur.

- A serious hypersensitivity reaction or anaphylaxis following SC usage of TCZ could occur in the home environment. Patients (and/or carers or other household members) may not be adequately prepared to deal with such an event, so there is the potential for delay in appropriate treatment which may, in the worst case scenario, result in a fatality. Patient specific safety and training materials need to be developed to address this.

First round assessment of benefit-risk balance

The benefit-risk balance of SC administration of TCZ is unfavourable given the proposed usage, but would become favourable if the changes recommended in the 'First round recommendations regarding authorisation' are adopted.

While comparable rates of injection site reactions, hypersensitivity reactions and anaphylaxis have been demonstrated for SC and IV administration of TCZ, the data for SC use is based on fewer PYs of follow-up and safety for home-based use has not been specifically presented. While the rates of serious hypersensitivity reactions and anaphylaxis following SC TCZ are low, it cannot be assumed that the outcomes for these events would be the same in the clinical and home environment. In clinical sites, access to professional assistance, resuscitation equipment and emergency drugs are usually readily available. The same cannot be said for a patient's home environment and delay in accessing appropriate treatment may result in an increased incidence of serious or fatal events.

First round recommendation regarding authorisation

The evaluator recommends:

> *Approval of the registration of a subcutaneous formulation of TCZ for the existing adult rheumatoid arthritis indication subject to modification of the PI (Patient Information), CMI (Consumer Medical Information) and RMP (Risk Management Plan).*

While there is a recognised potential for serious hypersensitivity reactions and anaphylaxis with the use of biologic agents, it is a rare event that can occur with any of the currently registered products. If an event occurs in the healthcare environment (the current situation with the IV formulation) appropriate treatment can be initiated immediately, ensuring the best chance for a full recovery. However, registration of the SC formulation will provide the opportunity for home use with no healthcare professional supervision. Under these circumstances, early signs of hypersensitivity may not be recognised resulting in treatment delays and an increased risk of adverse outcomes. Additionally non-serious hypersensitivity which, if recognised, would result in permanent discontinuation of treatment may not be appreciated by the patient resulting in continued use and an increased risk of a subsequent serious hypersensitivity reaction.

There are currently 5 biologic agents with SC formulations registered for use in adult patients with rheumatoid arthritis, four tumour necrosis factor (TNF) inhibitors: etanercept, adalimumab, certolizumab, golimumab and one T-cell co-stimulation blocker: abatacept. Each of these products has allergic reactions or hypersensitivity mentioned in the precautions section of the PI, but only abatacept reports a fatal case of anaphylaxis. Within the limitations of the data available, the incidence of anaphylaxis appears similar for the currently registered biologic agents with SC formulations and TCZ. However there have been deaths due to suspected severe allergic reactions on TCZ and a more conservative approach to home administration is considered appropriate. The 'Dosage and administration' section of the PI is therefore proposed to be modified such that the first 5 SC injections are administered under the supervision of a qualified healthcare

professional. This suggestion is based on the assumption that the distribution of anaphylaxis events following SC administration would reflect the distribution following IV infusion, and data from the Company Safety Database which demonstrated that 91% of anaphylaxis events following TCZ infusion (where the infusion number was known) occurred by Infusion number 5. This also reflects what occurred in the Phase III clinical trials of SC TCZ, where self-administration at home was allowed after 4 to 7 injections at the clinical site (including demonstrated competence in self-administration).

Clinical questions

Efficacy

1. The per protocol population was used for the longer-term analyses of efficacy (Week 49) for consistency with the Week 24 analyses reported in the Week 24 CSR, which were based on the PP population because WA22762 was a non-inferiority study. Please provide analyses for the efficacy variables presented in the CSR using the PP population to allow comparison with the Week 24 and 49 results.
2. It is noted that the ACR20/50/70 response rates at Weeks 24, 48/49, and 96/97 were similar for patients receiving SC TCZ weekly in Study WA22762 and SC TCZ 2 weekly in Study NA25220. Although these studies were not designed to be directly compared, the patient populations in these studies were similar (moderate to severe RA with an inadequate response to DMARDS). The dosage selection for the pivotal studies was based on PD profiles, however in view of the similar efficacy responses for the two dosage regimens, please comment on this finding and advise whether there are any planned or existing studies directly comparing clinical outcomes for the two SC dosing regimens.
3. The sponsor has stated that the final CSR for Study ML28338 would be provided for evaluation. In the Summary of Clinical Safety Addendum it was stated that the CSR 'is still in preparation'. If available, the sponsor is requested to provide this report for evaluation.

Safety

4. While the majority of anaphylaxis events occur with the first 4 to 5 infusions, similar data has not been reported for other hypersensitivity reactions. Please provide these data (for all hypersensitivity, clinically significant hypersensitivity, and serious hypersensitivity events) for Studies WA22762 and NA25220.
5. Based on the application letter and submission data there has only been one case of adjudicated anaphylaxis to SC TCZ up to 10 October 2014. It is not clear from the Drug Safety Report (with a data cut-off of 10 April 2013) whether this case forms one of the 122 adjudicated cases, or arose after the cut-off date. Please clarify this, and provide details regarding how many of the 732 potential anaphylaxis cases and 122 adjudicated anaphylaxis cases were on SC TCZ.
6. While the clinical trial protocols all allowed home administration after demonstrated competence in self-administration (or administration by a caregiver) at the clinical site, AEs have only been reported separately for the Japanese study (MRA229JP) for patients before and after the start of self-injection. Please provide information for Studies WA2262, NA25220 and ML28338 regarding the number of patients who administered SC TCZ at home, when this took place (after how many visits), and the amount of PYs of exposure to SC TCZ at home, self-injection at the clinical site, and healthcare practitioner injection at the clinical site. Please also provide information on the occurrence of hypersensitivity reactions and anaphylaxis for each of these

exposure periods. Where possible, please also provide this information for the post marketing data.

Second round evaluation of clinical data submitted in response to questions

See Attachment 2 for details of the sponsor's responses and the evaluator's comments on these responses.

Second round benefit-risk assessment

After consideration of the responses to clinical questions, the benefits of SC administration of TCZ in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of SC administration of TCZ in the proposed usage are essentially unchanged from those identified in the first round assessment of benefits.

Additional data on rates of injection site reactions and hypersensitivity reactions after home based administration were presented for Studies WA22762, NA25220, and ML28338. Overall, the majority of injections were administered at home (62.4%), and most of these were self-administered by the patient (78.2%). The number and rate of hypersensitivity events associated with home injections was much lower than for clinic injections, which is consistent with the facts that hypersensitivity events occur most frequently after the first 1 to 3 injections, and that per protocol, administration of the first 4 to 7 injections occurred in the clinic. While the potential for a serious hypersensitivity or anaphylactic reaction to occur after home based administration remains, the evidence presented to date (> 70,000 home based SC injections in clinical studies, and an estimated cumulative 34,413 patients on SC TCZ in the post authorisation phase) suggests that the risk is low and consistent with the risk for other biologic agents with SC formulations registered for use in adult patients with rheumatoid arthritis.

Second round assessment of benefit-risk balance

The benefit-risk balance of SC administration of TCZ is favourable given the proposed usage. The SC formulation of TCZ 162 mg weekly has demonstrated non-inferiority to the approved IV dosing regimen (8 mg/kg IV 4 weekly), and has a comparable safety profile. The risk of a serious hypersensitivity or anaphylactic reaction occurring in the home appears to be low, and is comparable to the risks associated with the SC formulations of other registered biologic agents.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted the following Risk Management Plan (EU-RMP (Version: 16.3, dated December 2014) with an Australian Specific Annex (ASA) Version: 4.0, dated 9 February 2015.

Safety specification

The sponsor provided the following summary of the ongoing safety concerns with Actemra (Table 11) as well as missing information, potential risks and interactions as specified in the ASA (Table 12).

Table 11: Sponsor provided summary of the safety issues as specified in the ASA.

Classification of risk	Risks identified
Important identified risks	Serious infections
	Complications of diverticulitis (including GI perforations
	Serious hypersensivity reactions
	Neutropaenia
Important potential risks	Neutropaenia and potential risk of infections
	Thrombocytopaenia with potential risk of bleeding
	Liver enzyme and bilirubin with potential risk of cerebrovascular events
	Malignancies
	Demyelinating disorders
	Immunogenicity
Paediatric patients	**Risks identified**
Important identified risks	Serious infections
	Serious hypersensitivity reactions
	Neutropenia
Important potential risks	Malignancies
	CYP450 enzyme normalisation
	Immunogenicity
	Skeletal development
Important missing information	Macrophage Activation Syndrome (MAS) in sJIA patients

Table 12. Sponsor provided summary of the missing information, potential risks and interactions as specified in the ASA.

Potential problem	Issue
Missing information	Data in elderly patients
	Data in paediatric patients
	Effects during pregnancy
	Hepatic impairment
	Renal impairment
	Combination with biologics
	Safety in patients < 60 kg in patients switching from IV to SC or SC to IV
	Long term data in patients switching routes of administration
	IgE data following TCZ SC treatment
Interations (identified and potential)	CYP450 enzyme normalisation

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information, including guided questionnaires for all the specified important identified and potential risks (except for 'immunogenicity', 'skeletal development (paediatric patients)' and 'CYP450 enzyme normalisation').

In comparison to the pharmacovigilance plan previously accepted for Actemra, the following changes have been observed:

- For the important potential risk: 'Immunogenicity' and the missing information: 'IgE data following TCZ SC treatment', the completed Studies WA22762 and NA25220 have now been included as additional pharmacovigilance activities. Final 2-year study reports for these pivotal Phase III studies were submitted in support of the current application.
- For the important potential risk: 'Skeletal development (paediatric patients)' and the missing information: 'Paediatric patients', a revised draft proposal for the Paediatric PcJIA patient registry (WA29358) was sent to the EMA in November 2014. A copy of this revised draft proposal is included in the ASA.
- For the important identified and potential interactions: 'CYP450 enzyme normalisation', the completed Study NP22775 to investigate the effect of TCZ on the pharmacokinetics and pharmacodynamics of an oral contraceptive in female patients with active RA has been deleted.
- The sponsor proposes routine pharmacovigilance activities to monitor the new missing information related to the SC formulation: 'Safety in patients < 60 kg in

switcher population', 'Long-term safety in patients in the switcher patient population' and 'IgE data following TCZ SC treatment'.

- The sponsor proposes to further characterise the new missing information related to the SC formulation: 'Safety in patients < 60 kg in switcher population' and 'long-term safety in patients in the switcher patient population' using epidemiology data from the EU registry (BSRBR).
- Updates to estimated availabilities of Clinical Study Reports for studies referenced in the RMP.

Risk minimisation activities

Planned actions

Routine risk minimisation activities will comprise labelling, including pharmacokinetic data, precautionary statements, instructions for use and notification of drug interactions and/or undesirable effects for all the specified safety concerns and missing information are sufficient, except for the important potential risk: 'Skeletal development (paediatric patients)' and the missing information: 'Safety in patients < 60 kg in switcher population', 'Long-term safety in the switcher patient population' and 'IgE data following TCZ SC treatment' for which no risk minimisation is proposed.

In the context of attaining approval for unsupervised home use of the SC formulation, the ASA states:

> *The sponsor intends to update the existing (additional risk minimisation) materials for intravenous Actemra in line with the information, precautions and instructions for using the new subcutaneous presentation. However, in line with how these materials are currently categorised these are not considered as an additional risk minimisation activity.*

In addition, the ASA states:

> *sJIA patients: sJIA patients are not permitted to receive Actemra under the ACTiv programme.*
>
> *pJIA patients: pJIA patients are not permitted to receive Actemra under the ACTiv programme.*

And:

> *sJIA patients receive infusions in hospitals as per condition of registration.*
>
> *pJIA patients receive infusions in hospitals as per condition of registration.*

Reconciliation of issues outlined in the RMP report

Table 13 (see below), provides a summary of the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and an evaluation of the sponsor's responses.

Table 13. Summary of recommendations in RMP evaluation report, sponsor's responses and evaluator's comments

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the clinical evaluator through the TGA's consolidated request for further information and/or the clinical evaluation report (CER). It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	In response to the CER comment: *'In addition, appropriate patient safety and training materials will need to be developed for review by the Pharmacovigilance & Special Product Access Branch'* the sponsor states: *'The sponsor wishes to clarify that the current additional risk minimisation materials (safety and training documents) for intravenous Actemra are intended to remain the same following the approval of the SC formulation. However, the sponsor intends to update the existing patient brochure and a patient safety card used in the information program for the new SC presentation'.*	This is contrary to the advice provided by the sponsor in the previous version of the ASA which stated: *'The sponsor intends to update the existing materials for intravenous Actemra in line with the information, precautions and instructions for using the new subcutaneous presentation'.* Nevertheless this new position is interpreted to mean that the existing additional risk minimisation activities for Health care Professionals (HCPs), which attempt to minimise the risk associated with management of possible hypersensitivity reactions occurring during or after an infusion of intravenous Actemra outside of the hospital setting, will remain as is. Subsequently the sponsor will now develop a new and separate suite of non-promotional educational materials for HCPs and patients in regard to the important identified risk: 'Serious hypersensitivity reactions' in the context of unsupervised home use of the subcutaneous formulation. Unfortunately the updated ASA has not been amended to reflect these changes.
		Consequently the sponsor should adequately revise the ASA as follows in regard to the important identified risk: 'Serious hypersensitivity reactions' in the context of unsupervised home use of the subcutaneous formulation and in accordance with Section 3: 'Risk Minimisation Plan' of

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
		the ASA template (as found on the TGA website as of 4 May 2015), before this application is approved: · describe and provide detail about the additional risk minimisation activities to be undertaken in Australia; · provide copies of at least draft Australian HCP and patient educational materials to the TGA for review as attachments to the ASA; and · provide detail about how and when the evaluation of these additional risk minimisation activities will be undertaken and reported to the TGA.
2. The sponsor's approach to simply updating the existing additional risk minimisation materials for intravenous Actemra with the information, precautions and instructions for using the new SC presentation is only acceptable if TGA approval for unsupervised home use of the SC formulation is obtained. The PSPAB will be guided by the PMAB evaluation of the supporting clinical data as to whether additional risk minimisation activities are required for the important identified risk: 'Serious hypersensitivity reactions', as it relates to the subcutaneous presentation.	See *Recommendation 1*	See *Recommendation 1*
3. The sponsor should provide justification for the following identified differences between the EU and the proposed Australian routine risk minimisation	For the missing information: 'Paediatric patients', the sponsor states: *'The Australian PI section 'Precautions', Paediatric Use has been updated to include a statement on the*	This is acceptable. These issues remain outstanding for the Delegate's consideration.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
activities, or alternatively include such information in the Australian PI to enhance safe use of the SC presentation: · For the important potential risk: 'Immunogenicity', the ASA states: 'The AU PI does not include the EU SPC data on the rate of formation of IgE antibodies following TCZ SC'. · For the missing information: 'Paediatric patients', the ASA states: 'The SPC includes a specific statement that the subcutaneous formulation has not been studied in children'. · For the missing information: 'Safety in patients < 60 kg in switcher population', the ASA states: 'The AU PI does not include the EU SPC text on the effect on exposure on switching patients from TCZ IV to SC'. · For the missing information: 'Long-term safety in the switcher patient population', the ASA states: 'The AU PI does not include the EU SPC text on the effect on exposure on switching patients from TCZ IV to SC'. · For the missing information: 'IgE data following TCZ SC treatment', the ASA states: 'The AU PI does not include the EU SPC data on the rate of formation of IgE antibodies following TCZ SC'.	*absence of data with the subcutaneous formulation in subjects less than 18 years old. The existing text on the clinical data with intravenous ACTEMRA has been updated to specify the ACTEMRA formulation used in those studies'.* For the other issues the sponsor states: *'A justification for the absence of this text in the Australian PI has been added to the updated version of the Australian Specific Annex to the EU-RMP'.*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
4. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.	The sponsor states: *'The Sponsor acknowledges this comment from the RMP Evaluator'.*	This issue remains outstanding for the Delegate's consideration.

Summary of recommendations

Issues in relation to the RMP raised in the clinical evaluation report

The sponsor was asked to respond to safety considerations raised by the clinical evaluator through the TGA's consolidated request for further information and/or the clinical evaluation report (CER), in the context of relevance to the RMP. In response to the CER comment:

> *In addition, appropriate patient safety and training materials will need to be developed for review by the Pharmacovigilance & Special Product Access Branch*

the sponsor states:

> *The Sponsor wishes to clarify that the current additional risk minimisation materials (safety and training documents) for intravenous Actemra are intended to remain the same following the approval of the subcutaneous formulation. However, the sponsor intends to update the existing patient brochure and a patient safety card used in the information program for the new subcutaneous presentation.*

This is contrary to the advice provided by the sponsor in the previous version of the ASA which stated:

> *The sponsor intends to update the existing materials for intravenous Actemra in line with the information, precautions and instructions for using the new subcutaneous presentation.*

Nevertheless this new position is interpreted to mean that the existing additional risk minimisation activities for health care professionals (HCPs), which attempt to minimise the risk associated with management of possible hypersensitivity reactions occurring during or after an infusion of IV Actemra outside of the hospital setting, will remain as is. Subsequently the sponsor will now develop a new and separate suite of non-promotional educational materials for HCPs and patients in regard to the important identified risk: 'Serious hypersensitivity reactions' in the context of unsupervised home use of the SC formulation. The RMP evaluator has noted that the updated ASA has not been amended to reflect these changes.

Consequently, the sponsor should adequately revise the ASA as follows in regard to the important identified risk: 'Serious hypersensitivity reactions' in the context of unsupervised home use of the SC formulation and in accordance with Section 3: 'Risk Minimisation Plan' of the ASA template (as found on the TGA website as of 4 May 2015) before this application is approved:

- Describe and provide detail about the additional risk minimisation activities to be undertaken in Australia

- Provide copies of at least draft Australian Health Care Provider (HCP) and patient educational materials to the TGA for review as attachments to the ASA
- Provide detail about how and when the evaluation of these additional risk minimisation activities will be undertaken and reported to the TGA.

Comments on the safety specification (SS) of the RMP

Clinical evaluation report

The SS in the draft RMP is not entirely satisfactory and should be revised, having regard to the comments below. Comments relate to EU RMP (dated December 2014, Version 16.3) and the updated ASA (dated February 2015, Version 4.0).

The important potential risks section does not include a number of issues identified in the precautions section of the PI (see below). Consideration should be given to including these issues.

- Tuberculosis
- Vaccinations
- Viral reactivation
- Infusion reactions

In addition, appropriate patient safety and training materials will need to be developed for review by the PSPAB.

In the RMP, serious hypersensitivity reactions are listed as an important identified risk and the Sponsor states that they intend 'to update the existing materials (Safety and Training Manuals) for intravenous Actemra in line with the information, precautions and instructions for using the new subcutaneous presentation. However, in line with how these materials are currently categorised these are not considered as an additional risk minimisation activity.' However, these Safety and Training Manuals appear to be targeted towards healthcare professionals, not patients. Appropriate patient safety and training materials will need to be developed for review by the TGA.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA requests for further information the sponsor provided an updated ASA (Version 4.1, dated August 2015). Key changes from the versions evaluated in the First round are summarised below:

ASA	· Correction to table cross-references to EU-RMP · Update to Risk Minimisation Activities tables to include justifications for not including certain text in the Australian PI, that is included in the EU SPC · Scope of "Potential for Medication Errors" section broadened

A revised ASA should be provided as recommended above.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluator has advised that approval is recommended for the SC presentation of TCZ. It was noted that the administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. Batch release testing is not required as the active substance is unchanged and its stability in the new formulation has been established in stability studies. Monitoring of product quality will be conducted through the post-market surveillance program. A condition will be included to submit data on the first five batches.

Nonclinical

No new data was submitted for the resubmission of SC presentation of TCZ.

The evaluator advised in the previous submission that there were no objections to the registration of TCZ solution for SC injection. Nonclinical data were submitted on bioavailability and toxicity which showed bioavailability to be about 83.5%, similar to humans via the SC route, and injection site reactions were unremarkable. Given the anticipated systemic exposure was lower from the SC route than the IV route, then there were no additional toxicological concerns.

Clinical

The new clinical dossier included the following data:

- 2 open label extension SC studies to Weeks 96/97 (WA22762 (SUMMACTA) and NA25220 (BREVACTA))
- 1 open label extension study to Week 108 (Japanese study, synopsis only)
- 1 open label extension study in IV use
- 2 Periodic Benefit-Risk Evaluation Reports
- 1 drug safety report
- 1 research report on anaphylaxis based on health claims data

Pharmacology

The previously submitted pharmacology studies noted the following findings:

- Absolute bioavailability from SC route was 77% (clearance changing with concentration).
- Absorption was slower by the SC route with a median t_{max} of 48 hours compared to 2 hours by IV route. Absorption half-life was about 4 days.

- Both SC presentations had similar plasma concentration profiles but with high inter-subject variability. Bioequivalence between them was seen for AUC_{inf} but was slightly bioinequivalent for AUC_{last} (0.90-1.27) and C_{max} (0.94-1.27).
- Weight had a significant effect on clearance and volume of distribution. In simulations from the population PK analysis, clearance was decreased by 25% in a 40 kg person and increased by 43% in a 140 kg person.
- Thigh administration increased bioavailability by 10%.
- Pharmacodynamic outcomes were similar from SC and IV routes.
- A dose-finding study indicated similar effects on ACR20, 50 and 70 responses and CRP from once weekly and once fortnightly dosing but a better DAS28 response for once weekly, although not statistically significant.

The new pharmacology information notes the following findings:

- PK from the SUMMACTA OLE Study (Study WA22762) is consistent with the DB phase of the study with higher pre-dose TCZ plasma concentrations following 162 mg SC weekly administration compared with 8 mg IV every 4 weeks administration.
- PK from the BREVACTA OLE (Study NA25220) is consistent with the DB phase of the study, with both the PFS and AI SC presentations resulting in similar pre-dose TCZ concentrations.
- PD from the SUMMACTA OLE (Study WA22762) study is consistent with the PD from the DB phase of the study:
  - Mean sIL-6R levels were maintained and comparable in the SC and IV arms.
  - Mean CRP levels were maintained in the normal range for the SC and IV arms.
  - Mean ESR levels remained low for the SC and IV arms.
- PD from the BREVACTA OLE (Study NA25220) study is consistent with the PD from the DB phase of the study:
  - Mean sIL-6R, CRP and ESR levels were maintained longer term.
  - Mean sIL-6R, CRP and ESR levels were comparable in the PFS and AI SC arms.

Efficacy

Study WA22762 (SUMMACTA) previously submitted: This was a multicentre, multinational, randomised, DB , double dummy, parallel group, non-inferiority study comparing SC (162 mg weekly) to IV (8 mg/kg every 4 weeks) TCZ in combination with a non-biologic DMARD in 1,262 subjects with moderate to severe RA. The primary efficacy endpoint was ACR20 at Week 24 with non-inferiority of the SC compared to the IV considered established if the difference between them was above -12% for the lower limit in the 95% confidence interval. The trial population was appropriate for this indication and the non-inferiority margin was considered clinically acceptable to show a treatment difference. Patients were 83% female, aged 18 to 86 years and had similar baseline demographics, disease characteristics (mean tender joint count of 27 out of 68 joints and swollen joint count of 15 out of 66 joints) and concomitant DMARD use (about 80% in both groups were on methotrexate [MTX]). About 30% of patients in each group started new rheumatoid arthritis treatments during the study but these were evenly matched. The results showed non-inferiority was established with the ACR20 response in the per protocol population being 69.4% on SC versus 73.4% on IV (difference of -4.0%, 95% CI -9.2 to +1.2%) with the lower limit of the 95% CI being greater than the non-inferiority margin of -12%. The response over time was similar for the two groups. Secondary

efficacy endpoints showed no significant difference in ACR50/70, DAS remission, DAS28, HAQ-DI or SF-36 for SC versus IV. A non-statistically significant difference by weight group appeared with those ≥ 100kg having a lower response for ACR20 on SC (52.8%) but a higher response on ACR50 and ACR70, compared to IV dosing. Patients < 60 kg had no difference in ACR20 between SC and IV dosing but a lesser response on ACR50 and ACR70 for SC versus IV dosing.

Study WA22762 (SUMMACTA) new data

This final report presents open label efficacy data to Week 97 for the above study, with analyses exploratory in nature and no formal comparison between treatment arms. The study consisted of a 24 week DB period discussed above followed by a 72 week OLE period. At Week 24, patients from the SC arm were re-randomised in a ratio of 11:1 to SC and IV, respectively, whilst patients from the IV arm were re-randomised in a ratio of 2:1 to IV and SC. Of the 572 patients who completed Week 24 in the SC arm, 524 were re-randomised to SC TCZ and 24 to IV TCZ (SC to IV switch). Of the 564 patients who completed Week 24 in the IV arm, 377 were re-randomised to IV TCZ and 186 to SC TCZ (IV to SC switch). A good clinical practice violation occurred at a site in Lithuania however this site included 12 patients which was not thought to significantly impact the overall findings. The overall efficacy results indicated the ACR20 response rate was maintained and comparable in the SC and IV arms at Week 49 (79% versus 78%) and Week 97 (84% versus 83%) and maintenance of effect was also observed in patients who switched at Week 25 from IV to SC (84% and 89% at Weeks 49 and 97, respectively) or SC to IV (71% and 83% at Weeks 49 and 97, respectively), although the latter group started from a lower baseline and was based on a small number of patients. Response rates for ACR50, ACR70, HAQ-DI, and DAS28-ESR were maintained for the duration of the study, and comparable in each of the treatment arms. Patients weighing ≥ 100 kg had lower ACR20, ACR50, and ACR70 responses than those weighing < 60 kg and 60 to 100 kg for the SC and IV groups.

Study NA25220 (BREVACTA) previously submitted

This was a multicentre, multinational, randomised, double blind, placebo controlled, parallel group study comparing SC TCZ (162 mg every 2 weeks) to placebo in combination with a non-biologic DMARD in 656 subjects with moderate to severe rheumatoid arthritis. The trial population was similar to the previous study. Patients were 85% female, age 18 to 82 years and had similar baseline demographics, disease characteristics (mean tender joint count of 28/68 joints and swollen joint count of 18/66 joints) and previous DMARD use. The primary efficacy endpoint of ACR20 at Week 24 by ITT analysis was superior on TCZ at 60.9% versus 31.5% on placebo (difference of 29.5%, 95% CI 22 to 37%). The effect was maintained to Week 52. Secondary efficacy endpoints (ACR50/70, DAS28, DAS remission, CRP, HAQ-DI and SF-36) were all superior on TCZ compared to placebo. An effect by weight was seen with the ACR20/50/70 responses being all less for those ≥ 100 kg (ACR20: 38.5% on TCZ versus 27.3% on placebo).

Study NA25220 (BREVACTA) new data

This final report presents open label efficacy data to Week 96 for the above study. The study consisted of a 24 week DB period discussed above followed by a 72 week OLE period. From Week 12 to 24, escape treatment (TCZ 162 mg weekly) was allowed for patients in either arm who had < 20% improvement in swollen joint count and total joint count from baseline. This therapy was continued until the end of study (Week 96). At Week 24, all patients remaining in the study who had not received escape therapy were re-randomised to either TCZ SC auto-injector or PFS. During the OLE phase of the study there was potential for bias in reporting for all subjective endpoints. The ACR20 response rate was maintained in patients remaining on TCZ PFS at Week 48 (88%), Week 72 (85.4%), and Week 96 (81.1%). Maintenance of effect was also observed in patients who switched at Week 24 from TCZ PFS to TCZ AI (82.9%, 83.0%, and 82.4% at Weeks 48, 72,

and 96, respectively). In patients who switched from placebo PFS to TCZ PFS or TCZ AI, a rapid improvement in ACR20 response was seen reaching levels comparable to patients on TCZ for the entire duration of the study by about Week 32. Response rates for ACR50, ACR70, HAQ-DI, and DAS28 Remission (< 2.6) were maintained for the duration of the study (after an initial improvement for those originally on placebo), and were generally comparable in each of the treatment arms. Radiography assessments (mTSS) at Weeks 24 and 48 demonstrated less progression in patients initially randomised to TCZ compared with those initially randomised to placebo. Patients weighing ≥ 100kg had lower ACR20, ACR50, and ACR70 responses at Week 96 than those weighing < 60kg and 60 to100 kg.

Study MRA229JP previously submitted

This was a supportive, multicentre, randomised, double blind, double dummy, parallel group, non-inferiority study comparing SC TCZ (162 mg every 2 weeks) to IV TCZ (8 mg/kg every 4 weeks) in 346 Japanese subjects with RA. The primary efficacy endpoint was ACR20 at week 24 with non-inferiority of the SC compared to the IV considered established if the difference between them was < -18% for the lower limit in the 95% confidence interval. Patients were 83% female, age 20 to 75 years. The results showed non-inferiority was established with the ACR20 response being 79.2% on SC versus 88.5% on IV (difference of -9.4%, 95% CI -17.6 to -1.2%) with the lower limit of the 95% CI being greater than the non-inferiority margin of -12%. The time course of response for ACR20/50/70, ACR components and DAS28 was similar in both groups.

Study MRA229JP new data (synopsis only)

An 84 week OL phase compared 162 mg SC TCZ administered every 2 weeks via a PFS or AI. In the combined SC group, the Week 108 ACR20/50/70 response rates were 92.5%, 80.6%, and 61.6%, respectively, and the mean DAS28 score was 1.92. Self-injection was performed by 82 subjects using either the PFS or the AI. No major difference between the ACR 20/50/70 response rates or DAS28 scores were detected before and after the start of self-injection.

Study WA18696

This study was submitted as a condition of registration from the original evaluation of the IV formulation of TCZ and relates to IV administration of TCZ in patients with RA. In this long term extension study of 2,067 patients with moderate to severe RA, 60.6% of patients completed 264 weeks of study treatment. Treatment with 8 mg/kg IV TCZ demonstrated improvements in the signs and symptoms of RA, disease activity, and functional status. Clinical response improved over time and was subsequently maintained out to 5 years. At the end of the 264 weeks, 40.5% had achieved an ACR70 response and 57.4% had achieved DAS-28 clinical remission. The AE profile seen in this latest study analysis was considered to be consistent with the known safety profile of TCZ. No new safety signals were identified. There were 21 serious hypersensitivity events reported in 10 patients, the majority of which the evaluator did not consider were clinically consistent with hypersensitivity. Two anaphylactic reactions were reported.

Study ML28338

This was a multicentre open label, long term extension (LTE) study to evaluate safety (primary objective) and efficacy of SC TCZ in patients with moderate to severe RA who completed Studies WA22762 or NA25220 and met the Study ML28338 entry criteria (US patients only). Patients on SC TCZ continued either weekly or every 2 weekly treatment, while those patients from Study WA22762 who were on IV TCZ 8 mg/kg, switched to SC TCZ weekly therapy. Efficacy based on a number of validated measures was generally maintained throughout the study, although based on a decreasing number of patients.

Safety

The two pivotal studies had exposure to SC TCZ for up to 2 years. AE frequency was similar between SC and IV groups at an overall 88% on IV, 92% on SC, 81% on SC then IV switch and 87% on IV-SC switch groups from the SUMMACTA study with administration site AEs being more common on SC dosing (20.8%) and IV then SC switch (14.5%) patients than in the IV (12.0%) and SC then IV switch (8.3%) patients. AEs of special interest occurred at a similar rate in the continuous SC and IV arms. AEs of special interest mostly occurred at a similar rate per 100 patient years in the continuous SC and IV treatment arms. For example:

- infection and infestation events: 108.7 versus 105.6
- serious infection: 4.0 versus 3.9
- adjudicated malignancies (including NMSC AEs): 0.9 versus 0.7
- hypersensitivity reactions: 8.8 versus 14.8
- serious hypersensitivity reactions (reported as an SAE): 0.5 versus 0.2
- injection site reactions (ISRs): 26.1 versus 33.6

In the IV TO SC arm, injection site reactions were higher and hypersensitivity reactions lower than the continuous IV and SC arms but were otherwise similar. There was a trend towards higher AE rates and numerically higher infections in patients weighing ≥ 100 kg at baseline.

In the BREVACTA study, a similar proportion of patients had at least 1 AE in each of the treatment arms; infections and infestations were the most common (upper respiratory tract infections (URTIs)).

Deaths occurred in 10 patients in the SUMMACTA study, 4 each in the SC and IV treatment arms and 2 in the IV TO SC switch arm, 5 of the deaths (2 in SC, 2 in IV, 1 in the IV TO SC switch arms) were considered related to the study treatment. Deaths occurred in 9 patients in the BREVACTA study.

Serious AEs (SUMMACTA: 13% on IV and 14% on SC) and discontinuations due to AEs occurred at a similar rate with no apparent difference between the groups. Increases in hepatic transaminases were observed but at a similar rate in SC and IV groups (in SUMMACTA two patients had 3 serious hepatic AEs, both in the IV arm). Decreases in neutrophil and platelet counts also occurred at a similar rate in both groups. Neutralizing anti-TCZ antibodies occurred in 1.6% on SC versus 1.1% on IV in SUMMACTA (2 patients (both on SC TCZ) had positive anti-TCZ IgE antibodies, no patients had an anaphylactic or serious hypersensitivity reaction) and 1.9% on PFS in BREVACTA. In the Japanese study, anti-TCZ antibodies were detected in 6 of 173 (3.5%) patients in the SC TCZ group (all during the DB phase) and in 1 of 173 (0.6%) patients in the IV TCZ group (after switch to SC administration) during the 108 week study. IgE anti-TCZ antibodies were higher on SC than IV in the Japanese study with injection site reactions being more common in people positive for IgE anti-TCZ antibodies. Injection site reactions were more common on SC than IV (12.2% versus 2.4%) in SUMMACTA and more common in the TCZ PFS arm than in the TCZ PFS to AI switch arm (22.01 versus 15.60) in BREVACTA. In the Japanese study, the incidence rate of administration site reactions was higher after the start of self-injection, but the reactions were all mild, and none of the subjects discontinued self-injection owing to injection site reactions. Infections were similar between SC and IV. Serious infections were comparable in the SC and IV arms (3.95 versus 3.92 events per 100 PY, respectively) in SUMMACTA with rates numerically higher in the IV TO SC arm (6.65 events/100PY). BREVACTA had few serious infections, but the rate (events per 100 PY) was numerically higher in the TCZ PFS arm (3.96) compared with the TCZ PFS to TCZ

AI switch arm (1.89). The overall rate of adjudicated malignancy including non-melanoma skin cancer AEs was comparable in the SC, IV and IV TO SC arms of SUMMACTA.

Anaphylaxis and hypersensitivity

Study SUMMACTA

No anaphylactic events were identified. Hypersensitivity reactions (see Table 14 below) were lower in the SC arm than in the IV arm (8.78 (7.05, 10.81) versus 14.82 (12.30, 17.71) events per 100 PY). There were 10 events in the IV TO SC arm and 1 in the SC TO IV arm (3.91 (1.88, 7.19) versus 1.51 (0.04, 8.42) events per 100 PY). Most of the hypersensitivity reactions were not considered clinically significant (did not result in withdrawal from the study drug). Rates for clinically significant hypersensitivity events were comparable in the SC and IV arms (1.18 (0.61, 2.07versus 1.47 (0.76, 2.57) events per 100 PY). No clinically significant hypersensitivity events were reported for either switch arm. Seven hypersensitivity events were reported as an SAE: 5 in the SC arm and 2 in the IV arm (0.49 (95% CI: 0.16, 1.15) versus 0.24 (0.03, 0.88) events per 100 PY). Ten additional potential hypersensitivity events (5 each in the SC an IV arms) occurred more than 24 hours after study drug administration. Most hypersensitivity reactions occurred during the first 1 to 3 SC injections, but also occurred later on during the extension phase. 17.5% of hypersensitivity events following IV TCZ occurred after 12 or more infusions (around 12 or more months of exposure at 4 weekly dosing) whereas up to 50% of hypersensitivity events following SC TCZ occurred after 12 or more injections (around 6 or more months of exposure at every 2 weekly dosing). However, the definition of hypersensitivity used in this analysis is a conservative one and many of the events were not clinically consistent with hypersensitivity reactions.

Study BREVACTA

No anaphylactic events were identified (see Table 14) and only 1 clinically significant hypersensitivity reaction was reported (TCZ PFS arm). Overall, 36 hypersensitivity reactions were reported and while numerically higher in the TCZ PFS arm, rates were generally similar across the treatment arms with wide and overlapping 95% CIs. Five escape patients (2 (2.0%) in the prior TCZ arm and 3 (3.3%) in the prior placebo arm) had at least 1 hypersensitivity event.

Study MRA229JP

No anaphylactic reaction events were reported in the 84 week open label period during which all patients received SC TCZ. One severe anaphylactic reaction was reported following the second IV TCZ infusion in the DB phase of the study.

Study ML28338

No anaphylaxis or serious and/or clinically significant hypersensitivity events were reported. Six potential hypersensitivity events were reported (2.39 (95% CI 0.88, 5.20) per 100 PY).

The clinical studies required the first 4 to 6 injections to be in the clinic before home based use was allowed. An analysis of hypersensitivity events by home versus clinical use of SC TCZ indicated that the number and rate of hypersensitivity events associated with home injections was much lower than for clinic injections, which is consistent with the earlier finding that hypersensitivity events occur most frequently within the first 1-3 injections.

Table 14: Incidence rates of hypersensitivity events following SC injections at home versus clinic.

WA22762	TCZ SC QW (N=631) Clinic	TCZ SC QW (N=631) Home	Placebo SC QW (N=631) Clinic	Placebo SC QW (N=631) Home
Total exposure (PY)	359.23	749.69	109.67	149.98
All Hypersensitivity				
# of AEs	66	31	33	19
Rate (per 100PY)	18.37	4.14	30.09	12.67
(95% CI)	(14.21, 23.37)	(2.81, 5.87)	(20.71, 42.26)	(7.63, 19.78)
Clinically Significant Hypersensitivity				
# of AEs	10	2	2	3
Rate	2.78	0.27	1.82	2.00
(95% CI)	(1.33, 5.12)	(0.03, 0.96)	(0.22, 6.59)	(0.41, 5.85)
Serious Hypersensitivity				
# of AEs	2	3	0	1
Rate (per 100PY)	0.56	0.40	0	0.67
(95% CI)	(0.07, 2.01)	(0.08, 1.17)	(0.00, 3.36)	(0.02, 3.71)
Serious Clinically Significant Hypersensitivity				
# of AEs	2	0	0	0
Rate (per 100PY)	0.56	0	0	0
(95% CI)	(0.07, 2.01)	(0.00, 0.49)	(0.00, 3.36)	(0.00, 2.46)
NA25220	TCZ SC (QW and Q2W) N=647 Clinic	TCZ SC (QW and Q2W) N=647 Home	Placebo SC Q2W N=218 Clinic	Placebo SC Q2W N=218 Home
Total exposure (PY)	469.55	477.28	66.67	11.06
All Hypersensitivity				
# of AEs	40	8	12	0
Rate (per 100PY)	8.52	1.68	18.00	0
(95% CI)	(6.09, 11.60)	(0.72, 3.30)	(9.30, 31.44)	(0.00, 33.34)
Clinically Significant Hypersensitivity				
# of AEs	1	2	0	0
Rate (per 100PY)	0.21	0.42	0	0
(95% CI)	(0.01, 1.19)	(0.05, 1.51)	(0.00, 5.53)	(0.00, 33.34)
Serious Hypersensitivity				
# of AEs	1	0	0	0
Rate (per 100PY)	0.21	0	0	0
(95% CI)	(0.01, 1.19)	(0.00, 0.77)	(0.00, 0.00,5.53)	(0.00, 33.34)

Drug safety report on anaphylaxis

No cases of anaphylaxis have been reported in the ongoing clinical trial program to date for TCZ SC but for IV the overall incidence was 0.298% (0.198% in RA). The Roche safety database (ARISg) was searched for all cases within the anaphylactic reaction standardised MedDRA query plus preferred term 'hypersensitivity'. In total, 732 cases were identified, of which 122 cases were assessed by the external adjudicators as 'anaphylaxis to (Tocilizumab) TCZ' cases of which none involved SC TCZ. The remaining 610 cases were adjudicated as either not anaphylaxis or evaluable. With an estimated cumulative patient exposure to TCZ between April 2005 and April 2013 of 234,146 patients, the un-adjudicated anaphylaxis incidence proportion is 0.31% (732/234,146), and the externally

adjudicated incidence proportion is 0.052% (122/234,146). For the 122 adjudicated anaphylaxis cases (see Table 15 below) anaphylaxis events occurred most commonly on the second (36.9%) or third (18.0%) infusion, but 1 case followed the twentieth infusion (0.8%). Of anaphylaxis events where the infusion number was known (n = 95), 57% (n = 54), 80% (n = 76), and 91% (n = 86) occurred by infusion number 2, 3 and 5 respectively. Fatal anaphylaxis has been reported 4 times (3 confirmed).

Table 15. Anaphylaxis event by infusion number (N = 122 cases).

Infusion number	Number of events	% Including NR	% Excluding NR
1	9	7.4%	9.5%
2	45	36.9%	47.4%
3	22	18.0%	23.2%
4	8	6.6%	8.4%
5	2	1.6%	2.1%
6	2	1.6%	2.1%
7	2	1.6%	2.1%
9	1	0.8%	1.1%
10	1	0.8%	1.1%
13	1	0.8%	1.1%
15	1	0.8%	1.1%
20	1	0.8%	1.1%
Not reported (NR) if events were associated with infusion	27	22.1%	--
Grand Total	**122**	**100.0%**	**100.0%**

An updated search of the ARISg database (cut off 10 October 2014), showed the reporting rate for hypersensitivity cases was about double on SC versus IV, but serious hypersensitivity was about the same and anaphylactic reactions was also about the same to slightly less on SC (see Table 16 and 17 below). One non-fatal anaphylaxis event has been reported with SC TCZ which occurred after the cut-off of the Drug Safety Report.

Table 16. Global Safety Database: Global reporting proportions and rates of hypersensitivity in patients exposed to IV and SC TCZ (cut off 10 October 2014).

	IV [a] (N=403,018)	SC [b] (N=20,920)
Postmarketing exposure (PYs)	343,512	17,380
Hypersensitivity SMQ (Narrow)		
No. cases	2749	305
Reporting proportion (per 100 patients)	0.7	1.5
Reporting rate [95% CI] (per 100 PY)	0.8 [0.77, 0.83]	1.8 [1.56, 1.96]
PT hypersensitivity (serious events)		
No. cases	148	11
Reporting proportion (per 100 patients)	0.04	0.05
Reporting rate [95% CI] (per 100 PY)	0.04 [0.04, 0.05]	0.06 [0.03, 0.11]

Table 17. Global Safety Database: Global reporting proportions and rates of anaphylactic reaction in patients exposed to IV and SC TCZ (cut off 10 October 2014).

	TCZ IV [a] (N=403,018)	TCZ SC [b] (N=20,920)
PYs exposure	343,512	17,380
Anaphylactic Reaction SMQ (Algorithmic)		
No. cases	701	23
Reporting proportion per 100 patients	0.17	0.11
Reporting rate [95% CI] per 100 PY	0.20 [0.19, 0.22]	0.13 [0.08, 0.20]

PT = preferred term. Cases for which the route of administration of TCZ was unknown or not IV or SC were excluded from the analysis. [a] Includes patients who received only IV or whose most recent administration of TCZ was IV. [b] Includes patients who received only SC or whose most recent administration of TCZ was SC.

Retrospective cohort study

The sponsor also conducted a retrospective cohort study of anaphylaxis in multiple cohorts of RA patients treated with commonly used biological medicines which contains information on the Medicare population with supplemental insurance paid for by employers. For drugs administered via the IV route, the incidence rates were similar. For drugs given via SC route (TCZ SC was not included), rates were generally comparable across the individual drugs although the point estimates were higher for certolizumab (0.93) and abatacept (0.58) for the sensitive definition.

PSURs

Two PSURs (PBRERs) were provided and the safety profile of SC TCZ was found to be comparable with the safety profile of IV TCZ (with the exception of injection site reactions which were more common with SC TCZ) (see Table 18 below).

Table 18. PBRER cumulative rates of serious hypersensitivity reactions, (11 April 2014 to 10 October 2014).

	Events per 100 PY (95% CI)	
	IV all exposure population (02 May 2012)	**SC all exposure population** (4MSU† Data Cut October 2012)
Rates of Serious Hypersensitivity‡	0.27 (0.20, 0.36)	0.37 (0.14, 0.81)
Rates of Anaphylaxis	0.05 (0.02, 0.10)	0 (0.00, 0.23)

† Four-Month Safety Update; ‡Serious hypersensitivity events were defined as all SAEs that occurred during or within 24 hours of a dose and which were not judged 'unrelated' to treatment by the investigator, regardless of whether or not they were consistent with hypersensitivity.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval for the SC presentation for all RA indications and for home based use as requested by the sponsor. The evaluator commented that the risk of a serious hypersensitivity or anaphylactic reaction occurring in the home appears to be low, and is comparable to the risks associated with the SC formulations of other registered biological medicines. The evaluator recommended the risk of serious hypersensitivity reactions and anaphylaxis in the home should be clearly communicated to both healthcare professionals and patients, and patients need to be educated regarding the symptoms and signs of allergic/hypersensitivity reactions to TCZ

so that appropriate action can be taken promptly, thus minimising potential adverse outcomes.

Risk management plan

An acceptable RMP/ASA has not been provided and the sponsor will need to satisfactorily address this matter with the RMP section before this submission can be finalised.

The following were outstanding matters and should be followed up with the TGA and in the Pre-ACPM Response where required:

- The sponsor was asked to respond to safety considerations raised by the clinical evaluator through the consolidated request and/or the CER, in the context of relevance to the RMP. In response to the CER comment: "In addition, appropriate patient safety and training materials will need to be developed for review by the Pharmacovigilance & Special Product Access Branch" the sponsor states: '*The Sponsor wishes to clarify that the current additional risk minimisation materials (safety and training documents) for intravenous ACTEMRA are intended to remain the same following the approval of the subcutaneous formulation. However, the Sponsor intends to update the existing patient brochure and a patient safety card used in the information program for the new subcutaneous presentation*'.

This is contrary to the advice provided by the sponsor in the previous version of the ASA which stated:

> *The sponsor intends to update the existing materials for intravenous Actemra in line with the information, precautions and instructions for using the new subcutaneous presentation.*

Nevertheless this new position is interpreted to mean that the existing additional risk minimisation activities for HCPs, which attempt to minimise the risk associated with management of possible hypersensitivity reactions occurring during or after an infusion of intravenous Actemra outside of the hospital setting, will remain as is. Subsequently, the sponsor will now develop a new and separate suite of non-promotional educational materials for HCPs and patients in regard to the important identified risk: 'Serious hypersensitivity reactions' in the context of unsupervised home use of the SC formulation. The RMP evaluator has noted that the updated ASA has not been amended to reflect these changes.

Consequently the sponsor should adequately revise the ASA as follows in regard to the important identified risk: 'Serious hypersensitivity reactions' in the context of unsupervised home use of the SC formulation and in accordance with Section 3: 'Risk Minimisation Plan' of the ASA template (as found on the TGA website as of 4 May 2015), before this application is approved:

- describe and provide detail about the additional risk minimisation activities to be undertaken in Australia;
- provide copies of at least draft Australian HCP and patient educational materials to the TGA for review as attachments to the ASA; and
- provide detail about how and when the evaluation of these additional risk minimisation activities will be undertaken and reported to the TGA.

Also refer to Recommendation 5 from the RMP/Pharmacovigilance section above.

Risk-benefit analysis

Delegate's considerations

The primary issues with this submission are as follows:

1. ACPM previously advised that home based use of SC TCZ should not be initially an option and that use should be in a healthcare facility. The Delegate accepted that advice and the sponsor subsequently withdrew the application to register SC TCZ. The sponsor has now re-submitted the application with additional data, analyses and an updated RMP to again request that the PI allow for SC use of Actemra in adults with rheumatoid arthritis in a home based setting.
2. ACPM previously advised that there was an overall positive benefit risk profile for the use of SC TCZ in patients with adult rheumatoid arthritis for the indications of combination use with MTX in patients who had failed a DMARD and to extrapolate the evidence to support monotherapy use in patients who had failed a DMARD. Since that advice, the sponsor has had an additional indication approved for the IV presentation of TCZ of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX. The sponsor is requesting that this indication also be approved for SC TCZ however there is no direct evidence to support it.

Proposed action

In the Delegate's summary and at the time of request for ACPM advice the Delegate had:

> *'No reason to say, at this time, that the application for Actemra should not be approved for registration, providing an acceptable RMP/ASA is agreed with the TGA.'*

Request for ACPM advice

The committee was requested to provide advice on the following specific issues:

1. Is the proposal to allow for self-injection at home of SC TCZ for adults with rheumatoid arthritis acceptable and are the related measures and statements outlined in the PI/CMI/RMP also acceptable?
2. Is it acceptable to extrapolate the evidence from the submitted data or has the sponsor provided sufficient justification to support the use of SC TCZ for the current (intravenous) indication of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Comment on the delegate's proposed action

The sponsor agreed with the Delegate's preliminary assessment that the application to register subcutaneous Actemra (TCZ SC) should be approved for registration provided an acceptable RMP/ASA was agreed with the TGA.

Comment on the delegate's overview

The sponsor agreed with the clinical evaluator's conclusion and Delegate's preliminary assessment that TCZ SC is appropriate for home use under the conditions specified in the

draft PI together with appropriate additional risk minimisation measures. The proposed PI states the first TCZ SC injection should be performed under the supervision of a qualified healthcare professional and after proper training in the injection technique, patients may self-inject with TCZ SC if their treating healthcare professional determines that this is appropriate. The proposal for home use is supported by the following key arguments.

No anaphylaxis and overall low incidence of hypersensitivity observed in clinical studies

In core studies WA22762 and NA25220, the long term extension rollover Study ML28338 and Japanese study MRA229JP, no anaphylaxis occurred in approximate 1800 RA patients treated with TCZ SC for up to longer than 3 years. Even with a conservative approach of applying a broad definition of hypersensitivity in these studies, the rates of hypersensitivity events, especially serious or clinically significant hypersensitivity, were low; most of the events were not medically consistent with hypersensitivity. Hypersensitivity events most frequently occurred at the first TCZ SC injection in the core Studies WA22762 and NA25220.

Low risk of hypersensitivity observed from extensive home use in clinical studies

Although the Phase III studies (WA22762, NA25220 and ML28338) required the first 4 to 6 injections to be in the clinic before home use was allowed, a large number of SC injections (> 70,000) were administered at home, mostly (78%) by patients themselves. The majority of patients (85 to 94%) received at least one SC injection at home, with an average of 25 to 48 injections per patient given at home. An analysis of hypersensitivity events by home versus clinical use of TCZ SC in Phase III studies provided with the sponsor's responses indicated that the number and rate of hypersensitivity events associated with home injections was much lower than that from clinic injections. This is consistent with the observation that hypersensitivity events occur most frequently within the first 1 to 3 injections.

Similar low risk of anaphylaxis from TCZ to other marketed biologics approved for home use the sponsor's retrospective study of anaphylaxis in multiple cohorts of RA patients indicated that the incidence of anaphylaxis from TCZ treatment appears similar to those from the currently registered biologic rheumatoid arthritis therapies for home use, including all tumour necrosis factor (TNF) inhibitors and the T-cell co-stimulation blocker abatacept.

Low risk of anaphylaxis from TCZ SC based on global post-market experience

TCZ SC has been approved in numerous overseas regions including Japan, US, EU, Canada, Switzerland and New Zealand. As of 31 October 2015, out of the cumulative total of 98 SC cases received and sent to external adjudication for anaphylaxis, only one (non-fatal) anaphylaxis ([information redacted]) was adjudicated as attributed to TCZ SC. This is the same case that was reported to the TGA in the sponsor's earlier communications. The sponsor continues the effort to monitor anaphylaxis cases.

Conclusion

Taking all evidence together, the sponsor's proposal of allowing home use after the first TCZ SC injection performed under the supervision of a qualified health is considered appropriate. The risk of serious hypersensitivity can be mitigated primarily by instructions provided in the PI and CMI. In addition, the sponsor planned to implement Educational Materials (EM) to re-enforce important safety information and instructions for correct use of the medicine. The proposed measures are consistent with those outlined in the approved prescribing documents in the EU, Japan, Canada, USA, New Zealand and Switzerland. The proposed administration instructions are similar to those of other SC biological medicines for RA approved for home use in Australia.

Responses to delegate's requests

'Please summarise the specific risk management activities that will be undertaken for home based use of SC TCZ, e.g. educational materials, etc., that address the potential for:

1. *hypersensitivity reactions and anaphylaxis in the home*
2. *communication to both healthcare professionals and patients on the symptoms and signs of allergic / hypersensitivity reactions to TCZ.'*

Risk minimisation for the identified risk of serious hypersensitivity reactions will be implemented with precautions and directions for use of the SC product in the PI and CMI (routine risk minimisation) and additional risk minimisation measures in the form of Educational Materials (EMs). In response to a request for Roche to use EMs from the TGA's RMP evaluation unit, the sponsor proposed to use a HCP brochure and a patient brochure. These EMs were under development but would be submitted to TGA before the application is approved. These EMs were already in use in the EU for TCZ and Roche proposes to develop materials locally which have similar content.

The Australian EMs will include important safety information and instructions for the correct use of the medicine. In terms of serious hypersensitivity reactions, the HCP EM will include:

- direction to assess the patient's suitability for home use, prior to home use occurring;
- instruction to inform patients they should seek immediate medical attention if they experience symptoms of a serious allergic reaction;
- direction that any patient showing a history of hypersensitivity to the product should not be rechallenged;
- instructions on the correct administration technique including diagrams;
- directions to refer to the full PI before prescribing.

The patient EM will also include general safety information about the product. Specific to the risk of serious hypersensitivity reactions it will include:

- instructions to inform their doctor of any allergies they may have prior to use and that they must not use the product if they have had an allergic reaction to TCZ SC;
- instructions on the correct administration technique including diagrams;
- while using the product, an emphasis that if they experience allergic reaction symptoms they should not administer the next dose until they have told their doctor and their doctor has said it is safe to do so;
- an instruction they should seek immediate medical attention if they experience symptoms of a serious allergic reaction;
- directions to read the CMI for more information.

In Australia, the sponsor proposed to distribute the EMs to target healthcare professionals via electronic means and via hard copy distribution. Distribution metrics are be reported to TGA annually to provide assurance that the EMs are being used and are widely distributed. In the EU, Roche has measured the effectiveness of the EMs by analysing the reporting rates of the AEs of special interest over time. The analysis indicates the reporting rates of AEs of concern have not increased over time. These stable reporting rates serve as a surrogate marker to show the EMs are well comprehended by the target HCPs.

3. *Please provide an update on the safety of SC TCZ from home based use overseas.*

Anaphylaxis

Relevant to the TGA's assessment of the proposal for home use, no new adjudicated anaphylaxis events attributable to TCZ SC has been identified since the sponsor provided an update in its response dated August 2015.

The sponsor identifies cases of anaphylaxis in the Global Safety Database through the Anaphylactic Reaction SMQ (algorithmic) as the search strategy. Identified cases are then sent to external adjudication to be assessed by a clinical panel of anaphylaxis experts. Roche has received a cumulative total of 98 cases of anaphylaxis from all sources for TCZ SC until 31 October 2015, and has sent them for external adjudication. Thirty one of these cases are still in the process of being adjudicated. Of the remaining 67 cases, 50 have been adjudicated as 'not anaphylaxis'. Of the remaining 17 cases, 8 have been adjudicated as anaphylaxis. The balance (n = 9) were adjudicated as 'unevaluable'. Of these 8 anaphylaxis cases, the relationship to TCZ was adjudicated as 'no' for 2 cases, unable to evaluate in another 2 cases, and as 'yes' in the remaining 4 cases. All of these 4 cases were switchers (SC to IV or IV to SC); in only one of them the anaphylaxis event had taken place while the patient was on SC. This is the same case that was reported to TGA within the sponsor's response dated August 2015.

Roche continues the efforts to monitor hypersensitivity and anaphylaxis cases and collect relevant information including the injection location (clinic, home and so on).

Periodic Benefit-Risk Evaluation Reports (PBRERs)

PBRERs for TCZ are issued once every six months; the latest PBRER is No. 1063698, issued on 10 June 2015. This PBRER was submitted to TGA on 16 June 2015 to continue to fulfil the product's condition of registration. New exposures figures will be available with the next 6 monthly report which is expected to be issued in the middle of December 2015.

No other, new or significant safety concern has been identified for the SC form (or TCZ in general) since the issue of the latest PBRER (10 June 2015).

4. *What is the rationale to support TCZ SC for the indication of 'Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX' given that no direct evidence has been submitted to support this indication? Why was TCZ SC not given this indication in Europe even though it was approved for IV TCZ?*

In the EU, the application for TCZ SC was submitted and approved prior to the indication extension was granted for early RA patients not previously treated with MTX. For that reason the early RA indication was not included in the initial TCZ SC approval in the EU. It was subsequently agreed with the EU Rapporteur and co-Rapporteur that a bridging strategy would be sufficient to support an early RA filing for TCZ SC without a dedicated study. The application for this indication for TCZ SC is expected to be submitted in November 2015.

Key evidence of PK, efficacy and safety from Studies WA22762 (SUMMACTA) and WA19926 (FUNCTION) indicates that a similar favourable benefit-risk profile from treatment of TCZ SC 162 mg weekly to TCZ IV 8 mg/kg every 4 weeks in early RA patients who are MTX naïve would be expected. The rationale is summarised below.

Overall bridging strategy

The pivotal Study WA22762 supports the current application to register TCZ SC and demonstrated that the efficacy and safety of TCZ SC 162 mg weekly was comparable to that of TCZ IV 8 mg/kg every 4 weeks in all patients diagnosed with RA at least 6 months prior to their first TCZ dose and who are in adequate responders to DMARD(s). The indication extension to early RA patients who are MTX naive for the IV formulation was

supported by the results of the single pivotal Study WA19926. In order to facilitate the comparison of data between the early RA population from WA19926 and WA22762 study, Roche performed post-hoc analyses in a subpopulation of WA22762 patients with RA diagnosed ≤ 2 years of the first TCZ dose (defined as early RA patients).

In WA22762, consistent with all the patients enrolled (the 'All Patient' population), the baseline demographics and RA disease characteristic of early RA subpopulation were similar and balanced between TCZ SC and TCZ IV treatment groups. As expected, the mean RA disease duration from All Patients of WA22762 was longer than that from TCZ IV 8 mg/kg + MTX group of the early RA study (WA19926); however, the early RA subpopulation of WA22762 treated with either TCZ SC or TCZ IV was similar to that from WA19926. Therefore, key efficacy and safety data were compared among the following 5 treatment groups:

- WA22762: TCZ 162 mg SC weekly + DMARD (All Patients, n = 631)
- WA22762: TCZ 8 mg/kg IV every 4 weeks + DMARD (All Patients, n = 631)
- WA22762: TCZ 162 mg SC weekly + DMARD (Patients with RA ≤ 2 years, n = 131)
- WA22762: TCZ 8 mg/kg IV every 4 weeks + DMARD (Patients with RA ≤ 2 years, n = 127)
- WA19926: TCZ 8 mg/kg IV every 4 weeks + MTX (All Patients, n = 290)

Pharmacokinetics

TCZ exposures summarised in WA22762 patients treated with TCZ SC by disease duration (RA ≤ 2 years, n = 132 versus RA > 2 years, n = 499) at baseline demonstrated the mean TCZ concentration over time up to Week 24 (end of the double-blind study period) in early RA patients was similar to that from patients with RA diagnosed > 2 years at baseline. Simulated steady-state TCZ exposures across body weight categories (< 60 kg, 60 to 100 kg, ≥ 100 kg) between patients with different disease duration also confirmed that the bioavailability of TCZ SC in early RA patients was expected to be comparable regardless disease duration and body weight categories.

Efficacy

As presented in Table 19, key endpoints at Week 24 (primary analysis time point for both WA22762 and WA19926) in intent to treat (ITT) population indicated that clinically meaningful efficacy that was observed in All Patients was also seen in the WA22762 early RA patients treated with both TCZ SC and TCZ IV. In WA22762, the efficacy responses in early RA patients treated with TCZ SC were similar to those in All Patients. The higher hurdle efficacy endpoints in WA19926 TCZ IV 8 mg/kg + MTX showed numerically stronger improvements than all groups from WA22762; this was possibly due to the fact that WA19926 patients were naïve to MTX and biologic DMARDs at study entry. The efficacy at Week 97 (WA22762) and Week 104 (WA19926) was sustained consistently in all treatment groups from both studies.

Table 19. ITT data for key efficacy endpoints (Week 24) for Study WA22762 and Study WA19926.

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ SC N = 631	TCZ IV N = 631	TCZ SC N = 132	TCZ IV N = 127	TCZ IV N = 290
ACR20, n (%)	427 (67.7)	443 (70.2)	90 (68.2)	97 (76.4)	216 (74.5)
ACR50, n (%)	287 (45.5)	294 (46.6)	62 (47.0)	74 (58.3)	165 (56.9)
ACR70, n (%)	149 (23.6)	167 (26.5)	37 (28.0)	42 (33.1)	112 (38.6)
DAS28 < 2.6, Remission, n (%)	217 (34.4)	205 (32.5)	47 (35.6)	49 (38.6)	130 (44.8)

Although radiographic endpoint was not investigated in WA22762, the improvement of radiographic endpoints observed after TCZ SC every 2 weeks dosing in NA25220 (BREVACTA) can also be expected in patients treated with a higher TCZ SC dose (weekly). Addition evidence to support an early RA indication for TCZ SC can be drawn from a study of TCZ SC in Japanese patients included within this re-submission filing (MRA229JP). Further analysis of efficacy in early RA subgroup patients of Study MRA229JP confirmed the efficacy following TCZ SC in a monotherapy setting.

Safety

As presented in Table 20, the overall safety profile is similar between TCZ SC and TCZ IV both in the early RA subpopulation as well as All Patients of WA22762. The rates of all AEs, SAEs and deaths from the TCZ IV 8 mg/kg + MTX patients of WA19926 was also within the range from those of WA22762. No anaphylaxis and low rates of serious hypersensitivity were observed in all 5 treatment groups. The rates of SAEs of special interest (for example, infections, malignancies, strokes, myocardial infarction, bleeding, hepatic events, gastrointestinal perforation) and occurrence of lab abnormalities were generally similar among treatment groups.

Table 20. Safety overview as AE, SAE and death rates per 100 PY (Study WA22762 and Study WA19926)

	WA22762				WA19926
	All Patients		Early RA Patients		
	TCZ SC N = 631	TCZ IV N = 631	TCZ SC N = 131	TCZ IV N = 127	TCZ IV N = 290
Exposure (PY)	1013.26	816.53	210.29	160.60	487.94
AE Rate per 100 PY 95% CI	415.89 [403.42, 428.64]	408.56 [394.81, 422.66]	371.87 [346.26, 398.87]	401.00 [370.63, 433.21]	353.32 [336.84, 370.40]
Death Rate per 100 PY 95% CI	0.39 [0.11, 1.01]	0.49 [0.13, 1.25]	0.00 [0.00, 1.75]	0.62 [0.02, 3.47]	0.82 [0.22, 2.10]
SAE Rate per 100 PY 95% CI	14.61 [12.35, 17.16]	15.43 [12.85, 18.37]	7.61 [4.35, 12.36]	13.08 [8.09, 19.99]	12.09 [9.20, 15.60]

In Study MRA229JP, the safety in the early RA subgroup patients was also generally similar to that from full population following TCZ SC in a monotherapy setting.

Conclusion

The key results from analyses of the full populations and subgroups of early RA patients in WA22762, and patients treated with TCZ IV 8 mg/kg + MTX of WA19926 provided sufficient evidence to demonstrate that a favourable benefit versus risk profile is expected

in early RA patients who are MTX naive following treatment of TCZ SC 162 mg weekly, although a dedicated study has not been conducted. TCZ SC 162 mg weekly is considered as the most appropriate matching dose of the approved TCZ IV 8 mg/kg every 4 weeks in early RA patients who are MTX naive either in combination with DMARD(s) or in a monotherapy setting.

5. *The sponsor should confirm if the CMI is included in the packaging or how will patients be provided with the information on SC injections in a home setting.*

As per the current legislated requirement, the PI will be the package insert. The sponsor does not intend to additionally include the CMI as a printed package insert as there are numerous other mechanisms for patients to access the CMI. For example, patients may obtain a printed copy from the pharmacist at the point of dispensing or via electronic sources such as the TGA website or the sponsor's Australian website.

As discussed in response to Question 1, Roche proposes to supplement the routine risk minimisation of the PI and CMI by implementing EMs: a HCP brochure and a patient brochure. The sponsor will distribute the EMs to target healthcare professionals via electronic means and via hard copy distribution. The patient brochure will re-enforce the key safety messages and directions for use from the CMI.

Advisory committee considerations

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Actemra solution for subcutaneous injection containing 162 mg/0.9 mL of tocilizumab to have an overall positive risk-benefit profile for the indication of:

> *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.*
>
> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX.*
>
> *In the two groups of patients above, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*
>
> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.*
>
> This presentation does not apply to the juvenile idiopathic arthritis indications.

In making this recommendation, the ACPM:

- Noted that the submission included an updated risk management and included instruction in the PI that allows for SC use of Actemra in the home base setting
- noted that the PI should advise that those > 100 kg may have a diminished response and that the weekly dosing is supported for those weighing < 100 kg
- advised that more detail on the hypersensitivity reactions for the RMP regarding anaphylaxis risk with home self-administration be included

- expressed concern that the risk of hypersensitivity reactions remained (although the level was low) and that appropriate resuscitation equipment is not often available in the home setting
- noted that the IV data indicate that the majority of anaphylaxis events occurred within the first five infusions
- advised that to mitigate the risk associated with anaphylaxis in the home setting when beginning to use SC Actemra, at least one injection should be supervised by a qualified health professional in a medical facility (with resuscitation facilities)
- advised that the physician ensure that the patient is aware of the signs of sensitisation and hypersensitivity and the importance of reporting these in a timely manner to the physician
- advised that home based use should not proceed until the physician is satisfied that the patient can safely inject and recognise and appropriately react to an anaphylactic reaction
- advised that post market follow up to check rates of anaphylaxis of IV versus SC use of Actemra should be provided to the TGA.

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Is the proposal to allow for self-injection at home of subcutaneous TCZ for adults with rheumatoid arthritis acceptable and are the related measures and statements outlined in the PI/CMI/RMP also acceptable?*

The committee advised that self injection at home of SC TCZ for adults with rheumatoid arthritis is acceptable if the following conditions are fulfilled:

- At the introduction of use of subcutaneous administration at least one injection is performed under the supervision of a qualified health care professional at a suitably equipped healthcare facility and after proper training in injection technique.
- The physician is satisfied that the patient is aware of the signs of sensitisation and will inform the medical practicioner should they occur.
- The physician is satisfied that the patient is capable of seeking appropriate assistance should early features of an anaphylactic response to an injection occur.
- Only when the physician is satisfied that the patient can safely inject in the home environment should the patient be encouraged to do so.

The committee advised that measures to support home administration of subcutaneous use of TCZ required amendments to the PI/CMI/RMP as follows:

- At least the first SC injection performed under the supervision of a qualified healthcare professional at a suitably equipped healthcare facility.

For the CMI

- The CMI should include advice regarding signs and symptoms of sensitisation and hypersensitivity reactions to assist the patient and caregiver in recognising them.
- The CMI should include a statement for advice on having someone else present during self-injection should in case the patient experiences a hypersensitivity reaction.
- The CMI should advise that there is a risk of anaphylaxis so that patients consider this when discussing home based use.

RMP: Materials for healthcare providers

- Directions to assesss patients for suitablility for home use.
- Instruction in educating patients that they should seek immediate medical attention if they experience symptoms of a serious allergic reaction.
- Any patient with a history of possible hypersensitivity should not be re-challenged.
- Correct administration technique.
- Full product PI.

2. *Is it acceptable to extrapolate the evidence from the submitted data or has the sponsor provided sufficient justification to support the use of SC TCZ for the current (intravenous) indication of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX?*

The committee agreed that there is sufficient justification to support the use of SC TCZ for the current (intravenous) indication of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Actemra solution for subcutaneous injection containing 162 mg/0.9 mL of tocilizumab to have an overall positive benefit–risk profile for the indication**:**

> *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.*
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> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors in combination with MTX in those not previously treated with MTX.*
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> *In the two groups of patients above, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*
>
> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.*
>
> This presentation does not apply to the juvenile idiopathic arthritis indications.

Specific conditions of registration applying to these goods

1. The Actemra EU-RMP Version 16.3 (dated December 2014, data lock point December 2014) with Australian Specific Annex Version 4.2 (dated January 2016) and any future updates, as agreed with the TGA will be implemented in Australia.
2. You [the sponsor] are to monitor for hypersensitivity reactions, including anaphylaxis, in the home based setting post-marketing and to report these, along with

comparative rates for IV and SC use, to the TGA in the Periodic Safety Update Reports required as part of the RMP.

3. Batch Release testing by OLSS: It is a condition of registration that, as a minimum, the first five independent batches of Actemra tocilizumab (rch) 162 mg/0.9 mL solution for injection pre-filled syringe (Prov AUST R 234034) imported into/manufactured in Australia are not released for sale until the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Attachment 1. Product Information

The PI approved for Actemra with this application is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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