Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tocilizumab

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Limited

June 2018

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
AAR52	Annualised relapse rate up to Week 52
ACR	American College of Rheumatologists
ADA	Anti-drug antibody
AE	Adverse events
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve (µg/mL day)
AUC,ss	Area under the concentration-time curve at steady state (mg/mL day)
AUCτ	Area under the concentration-time curve over dosing interval (mg/mL day)
BLQ	Below the limit of quantitation
BMI	Body mass index (kg/m^2)
BQL	Below the quantification limit
BSR/BHPR	British Society for Rheumatology/British Health Professionals in Rheumatology
Cave8	Individual predicted average concentration up to Week 8 from treatment start
CCD	Cumulative corticosteroid dose
CI	Confidence interval
CL	Non-specific time-independent clearance (L/day)
Cmax	Maximum drug concentration (mg/ml)
Cmax,ss	Maximum drug concentration (mg/ml) at steady state
CPH	Cox proportional hazards
CRP	C-reactive protein
CTA	Computed tomography angiography
Ctrough	Trough drug concentration (mg/ml)

Abbreviation	Meaning
Ctrough,ss	Trough drug concentration (mg/ml) at steady state
Ctrough52	Steady-state trough concentration at Week 52
CV	Coefficient of variation
CWRES	Conditional weighted residuals
DV	Observed TCZ concentrations
ELISA	Enzyme-linked immunosorbent assay
EQ-5D	EuroQol 5D health questionnaire
ER	Exposure-response
ESR	Erythrocyte sedimentation rate
EULAR	European league against rheumatism
FACIT-Fatigue	Functional assessment of chronic illness therapy fatigue
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
Fsc	Injection site on bioavailability
GCA	Giant cell arteritis
GI	Gastrointestinal
h	Hour/s
IBD	International birth date
IgG	Immunoglobulin G
II	Infections and infestations
IL-6	Interleukin-6
IND	Investigational new drug
IPRED	Individual prediction
ITT	Intent-to-treat
IV	Intravenous
ka	Absorption rate constant
LDL	Low-density lipoprotein
MCS	Mental component scores

Abbreviation	Meaning
mIL-6R	Membrane-bound interleukin-6 receptor
min	Minute/s
MRA	Magnetic resonance angiography
NPDE	Normalised prediction distribution errors
OFV	Objective function value
PBRERs	Periodic benefit-risk evaluation reports
PBO	Placebo
PCS	Physical component score
PD	Pharmacodynamics
PET-CT	Positron emission tomography-computed tomography
PGA-VAS	Patient Global Assessment – Visual Analog Scale
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMR	Polymyalgia rheumatica
popPK	Population pharmacokinetics
PRED	Population predictions
PSURs	Periodic safety update reports
Q	Inter-compartmental clearance
Q2W	Every other week
QW	Weekly
RA	Rheumatoid arthritis
REMI52	Remission up to Week 52
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	Short-Form 36 (Questionnaire)
sIL-6R	Soluble interleukin-6 receptor

Abbreviation	Meaning
sJIA	Systemic juvenile idiopathic arthritis
$t_{1/2}$	Half-Life
$t_{1/2}$, term	Terminal half-life
$t_{1/2}$,eff	Effective half-life
TAB	Temporal artery biopsy
TAD	Time after dose
TCZ	Tocilizumab
TFF	Time to flare
Vc	Central volume
Vp	Peripheral volume
VPC	Visual predictive check

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	14 November 2017
Date of entry onto ARTG	16 November 2017
Active ingredient(s):	Tocilizumab
Product name(s):	Actemra
Sponsor's name and address:	Roche Products Pty Limited Level 8, 30 – 34 Hickson Road, Sydney, 2000
Dose form(s):	Solution for injection
Strength(s):	162 mg/0.9 mL
Container(s):	Pre-filled syringe
Pack size(s):	Packs of 1 and 4 syringes
Approved therapeutic use:	*Giant Cell Arteritis (SC formulation only)* *Actemra is indicated for the treatment of giant cell arteritis (GCA) in adult patients*.
Route(s) of administration:	Subcutaneous (SC)
Dosage:	The recommended dose of Actemra for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.
ARTG number (s):	234034

Product background

This AusPAR describes the application by the sponsor to extend the indications of Actemra (tocilizumab or TCZ) for the treatment of *Giant Cell Arteritis (*GCA) in adults.

The proposed GCA indication would apply only for the subcutaneous formulation (162 mg/0.9 mL solution for injection pre-filled syringe).[1] This dosage form is currently available for the rheumatoid arthritis indications.

[1] 3 strengths of concentrated solution for intravenous infusion are available for the current approved indications but these dosage forms would not apply for the proposed GCA indication: 80 mg/4 mL injection concentrated vial (AUST R 149403), 200 mg/10 mL injection concentrated vial (AUST R 149404) and 400 mg/20 mL injection concentrated vial (AUST R 149402).

Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin IgG1 subclass which binds to human interleukin 6 (IL-6) receptors. The currently approved indications for Actemra in Australia are:

> *Rheumatoid Arthritis (IV and SC formulations): Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs.*
>
> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see 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 (IV formulation only): Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate (MTX). Actemra can be given alone or in combination with MTX.*
>
> *Systemic Juvenile Idiopathic Arthritis (IV formulation only): Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or in combination with methotrexate (MTX).*

Condition being treated

GCA is a chronic systemic vasculitis affecting large and medium sized arteries. 2 categories of GCA have been distinguished: (i) cranial GCA, involving the extracranial branches of the carotid arteries; and (ii) large vessel GCA, involving the aorta and its primary branches.[2] Cranial GCA is considered the most typical presentation, consisting of a broad spectrum of clinical and laboratory abnormalities that are attributable to ischaemia on one hand and systemic inflammation on the other. Common ischaemic complications include severe headache, scalp tenderness and jaw claudication. The most feared ischaemic complication is vision loss. Permanent vision loss affects approximately 15% to 20% of patients. Once vision loss is established, it is almost always permanent, but it can be prevented by early intervention.[3]

Large vessel GCA, which affects the aorta and its primary branches, particularly the subclavian, axillary and proximal brachial arteries, typically presents as vascular insufficiency to an extremity, for example, arm claudication or decreased/absent

[2] Weyand C and Goronzy J. Giant-cell arteritis and polymyalgia rheumatica. Ann Intern Med. 2003;139:505-515.

[3] Borchers A and Gershwin M. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev. 2012;11:A544-A554.

peripheral pulses.[4] Large vessel GCA can lead to aortic aneurysms; aortic dissection;[5] and coronary arteritis.[6]

The American College of Rheumatology (ACR) developed classification criteria for GCA based upon clinical, laboratory and histopathologic findings. The classification criteria were developed originally for the purpose of distinguishing GCA from other vasculitides.[7] GCA primarily affects adults who are 50 years of age or older and the risk for GCA increases with advancing age. The highest rates are observed in individuals between 70 and 79 years of age.[8] GCA incidence peaks from age 70 to 79 in women and > 80 years in men.

There is a significant increase in both incidence and prevalence with increasingly northerly latitudes with the highest incidence rates reported in Scandinavia and the United Kingdom at 20 to 30 cases per 100,000 people aged 50 years or older. By contrast, studies from southern Europe have consistently reported lower incidence rates at 7 to 10 cases per 100,000 people aged 50 years or older.[9] In the United States, GCA is most common in Caucasians of Scandinavian descent and is rare among African Americans.[9] In Olmsted County, Minnesota, US, the home of many Scandinavian immigrants, the annual incidence is 19.8 to 22.9 cases per 100,000 people aged 50 years or older.[10] GCA appears to be rare in Asian populations with a reported prevalence of 1.5 cases per 100,000 people in Japan.[11] It is unclear as to whether these changes reflect the different genetic backgrounds of the populations and/or additional environmental factors.

Current treatment options

GCA represents a medical emergency, requiring prompt diagnosis and initiation of treatment to prevent sudden vision loss and other ischaemic complications in patients with GCA.[12] The recommendations for GCA treatment, developed by European league against rheumatism (EULAR) and the British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR), are based on the current evidence and glucocorticoids are the cornerstone of treatment for GCA.[13,14,15]

---

[4] Brack A, et al. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum. 1999;42(2):311-7

[5] Warrington K and Weyand C. Giant Cell Arteritis and Polymyalgia Rheumatica.Oxford Textbook of Vasculitis. Ed: Ball, Fessler, Bridges. Chapter 2. 2014

[6] Butler N,et al. Aortic Complications of Giant Cell Arteritis: A Diagnostic and Management Dilemma. J Card Surg. 2010;25:572-581.

[7] HunderG, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33:1122-8.

[8] Petri H, et al. Incidence of giant cell arteritis and characteristics of patients: Data-driven analysis of comorbidities. Arthritis Care and Research. 2014;1-24

Gonzàlez-Gay M, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009;61(10):1454-61.

[9] Gonzàlez-Gay M, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009;61(10):1454-61. Watts R and Scott D. Epidemiology of vasculitis. Oxford Textbook of Vasculitis. Ed:Ball, Fessler, Bridges. Chapter 2. 2014. [11123]

[10] Chandran A, et al. The Incidence of Giant Cell Arteritis in Olmsted County Minnesota, Over a Sixty Year Period 1950 - 2009. Scand J Rheumatol. 2015;44(3):215-218.

[11] Kobayashi S, et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. Arthritis Rheum. 2003;49(4):594-8.

[12] Matteson E, et al. Glucocorticoids for Management of Polymyalgia Rheumatica and Giant Cell Arteritis. Rheum Dis Clin N Am. 2016;42:75-90.

[13] Mukhtyar C, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68:318-23.

[14] Borchers A and Gershwin M. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev. 2012;11:A544-A554.

[15] Dasgupta B, et al. BSR and BHPR Guidelines for the management of giant cell arteritis. Rheumatol. 2010:49:1594-1597.

Oral glucocorticoids (usually prednisone/ prednisolone) are initiated at a dose of 40 to 60 mg/day if a diagnosis of GCA is strongly suspected or confirmed by biopsy or imaging.[16] Patients with complicated GCA, for example those with evolving vision loss or history of amaurosis fugax , are often treated with intravenous (IV) methylprednisolone (500 mg to 1 g) daily for 3 days.[17] Once the clinical signs and symptoms of GCA have subsided, typically after 2 to 4 weeks, the glucocorticoid dose is gradually tapered. The decision to reduce glucocorticoids is based on the regular assessment of clinical signs and symptoms and evaluation of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels.

Although some patients can discontinue glucocorticoids after 1 to 2 years of treatment, up to 2 thirds of patients experience disease relapses upon tapering or after complete withdrawal of glucocorticoids.[18] Recurrence of disease after complete withdrawal of glucocorticoids occurs in more than 3 quarters of patients and is most often seen in the first year following completion of treatment.[19] In some patients with cranial GCA, the disease takes a relapsing chronic course requiring indefinite treatment with glucocorticoids.[20] Late vascular complications several years after a GCA diagnosis suggest that glucocorticoids doses sufficient to abate the signs and symptoms of cranial GCA may be inadequate to suppress or prevent vascular lesions in the large arteries. [20,21]

Although glucocorticoids are highly effective at inducing remission in most GCA patients, they are associated with a high toxicity burden, with 86% of patients experiencing glucocorticoid related AEs after 10 years of follow up, including bone fractures, avascular necrosis of the hip, diabetes mellitus, infections, gastrointestinal bleeding, cataracts and hypertension.[22] In a 15 year study of patients with GCA, 58% of patients had at least one serious glucocorticoid related adverse effect during their course of treatment.[16] Treatment with high dose glucocorticoids, especially in an elderly population, who commonly have multiple pre-existing comorbidities such as diabetes, hypertension and osteoporosis,

[16] Mukhtyar C, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68:318-23

[17] Mazlumzadeh M, et al. Treatment of Giant Cell Arteritis Using Induction Therapy With High-Dose Glucocorticoids. Arthritis Rheum. 2006;54:3310-3318

[18] Andersson R, et al. Long-term corticosteroid treatment in giant cell arteritis. Acta Med Scand. 1986; 220:465-9.

Alba MA, García-Marinez A, Prieto-González S, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine. 2014;93(5):194- 201.

Proven A, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703-8.

[19]Hoffman G, et al. A multicenter, randomised, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46(5):1309-18.

Hoffman G, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomised trial. Ann Intern Med. 2007;146(9):621-30.

[20] Borchers A and Gershwin M. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev. 2012;11:A544-A554.

[21] Nuenninghoff D, et al. Incidence and Predictors of Large-Artery Complication (Aortic Aneurysm, Aortic Dissection and/or Large- Artery Stenosis) in Patients With Giant Cell Arteritis. Arthr Rheum. 2003a;48:3522-3531.

[22] Nesher G, et al. Analysis of steroid related complications and mortality in temporal arteritis: A 15-year survey of 43 patients. Rheumatol. 1994;21:1283-1286.

Petri H, et al. Incidence of giant cell arteritis and characteristics of patients: Data-driven analysis of comorbidities. Arthritis Care and Research. 2014;1-24

Proven A, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703-8

Broder M, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis. Sem Arthr Rheum. 2016, in press.

carries serious risks.[23] Moreover, cases of sudden death from high dose IV glucocorticoids have been reported.[24]

Given the seriousness of glucocorticoid related adverse events (AEs), considerable efforts should be made to minimise the duration of treatment and the cumulative glucocorticoid dose. Other immunosuppressive drugs have been considered as alternatives to glucocorticoids (or to reduce the need for glucocorticoids), with limited information or evidence of success. However, no agents capable of maintaining disease remission once glucocorticoid therapy has been discontinued have been approved.

While glucocorticoids have established themselves as standard of care, there are currently no treatments approved specifically for the treatment of GCA. The Mayo Clinic, EULAR and BSR/BHPR guidelines recommend considering the immunosuppressive agent methotrexate as adjunctive therapy.[25] However, the available evidence for methotrexate in the management of GCA is limited and trials using methotrexate have yielded equivocal results.[26] A meta-analysis of individual patient data from these randomised controlled trials demonstrated a modest reduction in relapse and glucocorticoid exposure in the methotrexate treated groups.[27] However, a further meta-analysis of the same trials of methotrexate concluded there was no significant benefit.[28] Open label studies have explored the effects of cyclosporine A, leflunomide, mycophenolate mofetil, or cyclophosphamide in the treatment of GCA but the patient numbers were too small to draw firm conclusions.[29] Randomised clinical trials of tumour necrosis factor inhibitor (TNFi) agents, including infliximab, adalimumab and etanercept, have shown no efficacy in GCA.[30] A recent Phase II, randomised, double blind, placebo controlled and withdrawal design trial of the CTLA-4 inhibitor abatacept has shown some evidence of efficacy in the

[23] Weyand C and Goronzy J. Giant-cell arteritis and polymyalgia rheumatica. N Engl J Med. 2014;371(1):50-57.
[24] Gonzàlez-Gay M, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009;61(10):1454-61.
Mazlumzadeh M, et al. Treatment of Giant Cell Arteritis Using Induction Therapy With High-Dose Glucocorticoids. Arthritis Rheum. 2006;54:3310-3318.
[25] Warrington K and Weyand C. Giant Cell Arteritis and Polymyalgia Rheumatica.Oxford Textbook of Vasculitis. Ed: Ball, Fessler, Bridges. Chapter 2. 2014.
Mukhtyar C, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68:318-23.
Dasgupta B, et al. BSR and BHPR Guidelines for the management of giant cell arteritis. Rheumatol. 2010:49:1594-1597
[26] Hoffman G, et al. A multicenter, randomised, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46(5):1309-18.
Jover J, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;134(2):106-14.
Spiera R, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol. 2001;19(5):495-501.
[27] Mahr A, et al. Adjunctive Methotrexate for Treatment of Giant Cell Arteritis - An Individual Patient Data Meta-Analysis. Arthritis Rheum. 2007;56:2789-2797.
[28] Yates M, et al. Prednisolone combined with adjunctive immunosuppression is not superior to prednisolone alone in terms of efficacy and safety in giant cell arteritis: meta-analysis. Clin Rheumatol. 2014;33:227-236.
[29] Schaufelberger C, et al. No additive effect of cyclosporin A compared with glucocorticoid treatment alone in giant cell arteritis: results of an open, controlled, randomized study. Br J Rheumatol. 1998;37(4):464-5.
Sciascia S, et al. Mycophenolate mofetil as steroid-sparing treatment for elderly patients with giant cell arteritis: report of three cases. Aging Clin Exp Res. 2012;24(3):273-7.
Adizie T, et al. Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. Int J Clin Pract. 2012;66(9):906-9.
Quartuccio L, et al. Role of oral cyclophosphamide in the treatment of giant cell arteritis. Rheumatology. 2012;51(9):1677-86.
[30] Hoffman G, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomised trial. Ann Intern Med. 2007;146(9):621-30.
Seror R, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicenter randomised controlled trial. Ann Rheum Dis. 2014 Dec; 73(12):2074–81, Epub 2013 July 29.

treatment of GCA in 49 patients.[31] However, the difference in treatment response between active and control arms was not compelling and would require further substantiation in the setting of a larger, more rigorous randomised clinical trial.

The studies contained in the Australian dossier are the same as that submitted in the European Union (EU) and United States of America (USA), with the exception of the country specific requirements.

Regulatory status

Actemra was first approved in Australia in 2009 for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients.

In 2010 the indication was extended to include inhibition of the progression of joint damage, as measured by X-ray, when given in combination with methotrexate.

In 2011 the indication was extended to include systemic JIA in patients 2 years of age and older and in October 2013 for patients with polyarticular JIA.

In 2014, the RA indications were extended to include combination use with methotrexate in patients not previously treated with methotrexate.

In January 2016, a 162 mg weekly SC dosage regimen was approved for the RA indications, including approval for home based use.

SC and IV formulations of TCZ (under the trade names of Actemra or RoActemra) are approved in many countries (including the USA and the EU) for the treatment of moderate to severe rheumatoid arthritis (RA). The IV formulation is also approved for the treatment of systemic juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic arthritis (pJIA) in more than 75 countries globally, including the United States and EU countries, as well as for Castleman's disease in India and Japan.

In Australia, Actmera (TCZ) has been approved for treatment of moderate to severe active RA in adult patients in combination with MTX or other non-biological disease modifying antirheumatic drugs (DMARDs). Monotherapy with Actemra is approved in case of intolerance to MTX or where continued treatment with MTX is inappropriate.. Actmera is also approved in Australia as monotherapy or in combination with MTX for treatment of pJIA and systemic JIA (IV formulation only).

Similar applications for extension of indications to include treatment of GCA in adults have been approved in the EU, USA and Switzerland (see Table 1, below). In the USA, Actemra has been granted Breakthrough status in treatment of GCA. An evaluation is under consideration in Canada.

Table 1: International regulatory status

Region	Submission status	Approved indication
EU (Centralised procedure). Rapporteur: Germany; Co-rapporteur: Hungary.	Submitted: 17 November 2016 Positive CHMP opinion: 20 July 2017 EU registration: 18 September 2017	'RoActemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.'

[31] Langford C, et al. A Randomized Double-Blind Trial of Abatacept and Glucocorticoids for the Treatment of Giant Cell Arteritis [abstract]. Arthritis Rheumatol. 2015;67(suppl 10).

Region	Submission status	Approved indication
USA	Submitted: 22 November 2016 Approved: 22 May 2017 Breakthrough Therapy Designation was granted by FDA for Actemra for giant cell arteritis. The application was evaluated under Priority Review.	'Adult patients with giant cell arteritis.'
Canada	Submitted: 30 March 2017 Approved: 27 October 2017	Actemra is indicated for the treatment of giant cell arteritis (GCA) in adult patients.
New Zealand	Submitted: 9 December 2016 Approved: 1 June 2017	'Actemra is indicated for the treatment of giant cell arteritis (GCA) in adult patients.'
Switzerland	Submitted: 6 January 2017 Under evaluation	

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR 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. Registration timeline

Table 2: Registration timeline for Submission PM-2016-03548-1-4

Description	Date
Submission dossier accepted and 1st round evaluation commenced	3 January 2017
First round evaluation completed	29 May 2017
Sponsor provides responses on questions raised in first round evaluation	3 July 2017
Second round evaluation completed	9 August 2017
Request for Advisory Committee advice and/or Delegate's Overview	4 September 2017
Sponsor's response to Delegate's Overview	19 September 2017
Advisory Committee meeting	5 to 6 October 2017
Registration decision	14 November 2017
Entry onto ARTG	16 November 2017
Number of TGA working days from commencement of evaluation to registration decision *	194

III. Quality findings

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

IV. Nonclinical findings

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

V. 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

Elevated tissue and serum levels of IL-6 have been reported in the pathogenesis of GCA and correlate with disease activity. The pro-inflammatory, multifunctional cytokine IL-6 is produced by a variety of cell types, including T cells, B cells, monocytes, fibroblasts, keratinocytes and synovial and endothelial cells. IL-6 has been shown to be involved in diverse physiological processes, such as T cell activation, B cell differentiation, induction of

immunoglobulin secretion, acute phase protein production, stimulation of haematopoietic precursor cell growth and differentiation, osteoclast differentiation from precursor cells, proliferation of hepatic, dermal and neural cells, and bone and lipid metabolism.[32] It exerts its effects through the IL-6 receptor (IL-6R), which is present both in soluble and in membrane expressed forms. Its potential in the treatment of GCA stems from the putative role of IL-6 as a key cytokine in inflammation.

Tocilizumab is a recombinant humanised, anti-human monoclonal antibody of the IgG1 subclass. The molecule targets the soluble and membrane bound forms of the IL-6 receptor (sIL-6R and mIL-6R), adhering to the IL-6 binding site of these receptors and inhibiting IL-6 signalling in a competitive manner.

Following a compelling case study in 2010 , a number of additional case studies reporting a therapeutic benefit of TCZ in 31 GCA patients were published; 29 patients received 8 mg/kg IV every 4 weeks (in some cases the starting dose was 8 mg/kg every 2 weeks) and 2 patients received 4 mg/kg IV every 4 weeks. Positive treatment effects of TCZ in GCA were reported, showing consistent achievement of remission, low risk of flares during treatment, rapid glucocorticoid taper to low dose or complete withdrawal and good tolerability of TCZ.[33] Based on these observations, in 2012 the sponsor initiated a clinical development program based on a Phase III randomised, double blind, placebo controlled superiority study to evaluate SC TCZ in GCA. About the same time, a Phase II single centre, investigator initiated Roche supported trial was begun to study the IV formulation of TCZ in GCA patients; that study was unblinded prior to the completion of Part 1 of Study WA28119.[34]

Thus, inhibition of the biological activity of IL-6 by TCZ represents a promising new approach for the treatment of GCA.

Contents of the clinical dossier

Scope of the clinical dossier

The dossier documented a development program of pharmacology, dose finding, pivotal and other clinical trials relating to the proposed extension of indications:

- The PK and PD of TCZ in combination with a 26 week prednisone taper regimen in patients with GCA in the Phase III, multicentre, randomised, double blind placebo controlled Study WA28119.
- A population PK/PD analysis (PopPK), Study PopPK WA28119, in which a model was generated to explain TCZ concentration data collected over 52 weeks and included a tertile and graphical analysis of the exposure-response relationship of selected PD, efficacy and safety parameters collected over this period.

[32] Dayer J and Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. Rheumatology. 2010;49:15-24.

[33] Seitz M, et al. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. Swiss Med Weekly. 2011;141:w13156.

Salvarani C, et al. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. Rheumatology. 2012;51(1):151-6.

Unizony S, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. Arthritis Care Res. 2012;64(11):1720-9.

Christidis D, et al.. Successful use of tocilizumab in polymyalgic onset biopsy positive GCA with large vessel involvement. BMJ Case Rep. 2011.

Beyer C, et al. Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. Ann Rheum Dis. 2011;70:1874-5.

[34] Villiger P, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo controlled trial. Lancet. 2016;387:1921-27.

- Pivotal efficacy/safety study: A Phase III, multicentre, randomised, placebo controlled, double blind, parallel group superiority Study WA28119 (GiACTA) in patients with GCA designed to evaluate the safety and efficacy of TCZ for the treatment of GCA.

Other efficacy/safety studies submitted included:

- Study ML25676;[34] data from this study using IV TCZ was included to provide supportive evidence of efficacy/ safety of TCZ in treatment of GCA. However, the original CSR was not provided for evaluation;
- Real world evidence report: Analysis of oral glucocorticoid use over time, expected incidence rates of safety events of interest and risk associated with cumulative use of oral glucocorticoids in giant cell arteritis patients in marketscan; and
- Literature references.

Paediatric data

The proposed extended indication of Actemra is for treatment of GCA in adults only.

Good clinical practice

The pivotal Study WA28119 included in this application was conducted in accordance with the principles of the 'Declaration of Helsinki', the US FDA regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and applicable local, state and country laws. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved all studies.

Pharmacokinetics

The following table summarises the pharmacokinetic studies submitted (see Table 3).

Table 3: Studies providing pharmacokinetic data

PK topic	Subtopic	Study ID	*
PK in special populations	Target population§ - Multi dose	WA28119	PK and PD of TCZ in combination with a 26 week prednisone taper regimen in patients with GCA.
Population PK analyses	Target population	PopPK WA28119	Development of a popPK model using TCZ concentration data collected over 52 weeks from patients with GCA and which included a tertile and graphical analysis of the exposure-response relationship of selected PD, efficacy and safety parameters.

* Indicates the primary PK aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

- TCZ is a recombinant humanised anti-human monoclonal antibody, which is directed against the IL-6. It is to be administered once weekly via SC injection.
- The estimated absorption rate constant (Ka) and time of peak plasma concentration (T_{max}) of TCZ at steady state in patients with GCA is 0.193 Day 1 and 3 days, respectively.

- The bioavailability of the SC formulation of Actemra has been previously reported to be 0.8.
- In patients with GCA administered 162 mg SC doses of TCZ QW for 52 weeks, the mean (± SD) TCZ serum concentration was 67.93 ± 34.40 µg/mL, whereas, the pre-dose TCZ concentrations in responders and non-responders were 69.18 ± 35.00 µg/mL and 64.89 ± 33.51 µg/mL, respectively.
- The proposed weekly dosing with TCZ for treatment of GCA appears to be justified as TCZ exposure was considerably higher (approximately 5.5 fold) following administration once weekly (QW) compared once every 2 weeks (Q2W) as the mean TCZ concentration detected in GCA patients following 24 weeks of QW dosing and Q2W dosing were 68.18 µg/mL and 12.46 µg/mL, respectively.
- The estimated central and the peripheral volume of distributions of TCZ in patients with GCA were 4.09 L and 3.37 L, respectively.
- TCZ elimination is comprised of linear and non-linear clearance. At TCZ serum concentrations of around 50 µg/mL the 2 components contribute equally to TCZ elimination. Therefore, the half-life ($t_{1/2}$) of TCZ is also concentration dependent and the effective $t_{1/2}$ of TCZ at steady state was found to vary between 18.3 and 18.9 days for 162 mg SC QW regimen.
- The estimated inter-individual variance on clearance, ka, central volume (Vc) and peripheral volume (Vp) were 0.056, 0.174, 0.082 and 0.227, respectively, and the variance on the residual error was 0.129.
- The TCZ serum concentration data in patients with GCA was best described by a 2 compartment model with parallel linear and Michaelis-Menten elimination. The covariates included in the final model were: body weight on clearance (CL), Vc and Vp; age on ka and injection site (thigh) on bioavailability.
- The PK aspects of the proposed draft PI are satisfactory.

Pharmacodynamics

Studies providing pharmacodynamic data

Both of the new studies included in the evaluation materials that contain PD results also contain PK data and therefore have been summarised in Table 3 above.

Evaluator's conclusions on pharmacodynamics

- TCZ binds specifically to both soluble and membrane bound IL-6 receptors and has been shown to inhibit sIL-6R and mIL-6R-mediated signalling.
- Following the initiation of TCZ therapy in patients with GCA, sIL-6R levels increased over the initial 16 weeks of treatment, whereas, from Week 16 through to Week 52 sIL-6R levels were relatively stable. At Week 52, the sIL-6R levels were 29% higher in the TCZ QW group than in the TCZ Q2W group.
- IL-6 levels increased by approximately 14.3 fold over pre-dose levels following the initial TCZ dose; however by Week 52 the increase in IL-6 levels had diminished and levels were approximately 7.5 fold higher than baseline. At Week 52, IL-6 levels were 25% higher in the TCZ QW treatment group than in TCZ Q2W group. Following the initiation of treatment with TCZ, median CRP and ESR values decreased rapidly and remained low throughout the remainder of the study. In contrast to the TCZ treated

patients, sIL-6R, IL-6, CRP and ESR values were unchanged in subjects administered placebo.

- Analysis of the safety population for the development of anti-TCZ antibodies indicated that the incidence of treatment induced anti-drug antibodies (ADAs) was low: 1 (1.1%) and 3 (6.5%) patients for the TCZ QW and TCZ Q2W treatment arms, respectively. No patients experienced anaphylaxis, serious / clinically significant hypersensitivity reactions, Injection site reactions (ISRs) or withdrew due to a lack of efficacy. All 4 patients developed ADAs with neutralising potential but no patients had ADAs of the IgE isotype.
- 3 TCZ treated patients, all in the TCZ Q2W treatment arm, who demonstrated low or undetectable serum levels of TCZ developed treatment induced ADAs.
- 13 (5.3%) out of 245 patients who provided baseline samples were positive for baseline ADAs.
- 2 patients from the placebo groups were also positive for treatment induced ADAs.
- In all 6 patients that tested positive for either TCZ or placebo treatment induced ADAs, positive ADA titres were transient and in the TCZ population only occurred at study Weeks 24 and 36.
- In 2 patients, who were both receiving TCZ Q2W and were positive for treatment induced ADAs, TCZ concentrations appeared to show a transient decrease at the Week 24 visit when ADAs were detected but there was no sustained decrease at subsequent visits where ADA measures also became negative.
- Modelling of the time to first flare estimated that the risk of flare in males was approximately 3 times lower than in females and in patients receiving TCZ, where the 95th percentile of Cave8 was 48.6 μg/mL, the first flare hazard was reduced by 55%.
- Overall, the risk of flare was diminished considerably at lower TCZ exposure levels following QW than Q2W dosing (approximately 84% at the 5th exposure percentile), whereas, when higher TCZ exposure levels were achieved the difference between the risks of flare for the 2 dosing regimens was reduced.
- Graphical analyses undertaken as part of the PopPK study indicated that, in subjects administered TCZ, CRP and, ESR declined to and remained at low levels throughout the observation period, whereas, IL-6 levels increased (from approximately 10 pg/mL to 70 mg/mL) over the initial 2 to 4 weeks of treatment before declining to about 50 pg/mL and there were no meaningful differences in IL-6 levels between the 3 TCZ exposure groups. sIL-6R levels slowly increased and reached maximum levels 2 to 3 months after treatment initiation and, in contrast to IL-6, sIL-6R levels were increased as exposure to TCZ increased.
- There were no differences in the distributions of steady state trough concentration at Week 52 ($C_{trough,52}$) for patients in the active TCZ treatment arms who achieved and did not achieve sustained remission up to Week 52, nor was there a significant relationship between exposure and probability of remission up to Week 52(REMI52).
- The fraction of patients in remission was lowest in the placebo group and it was highest and similar in the 2 groups who experienced the highest exposure to TCZ. In the lowest TCZ exposure group, this fraction was similar to the placebo arm during the first 3 to 4 months of treatment but reached the remission rate of the other 2 exposure groups by the end of the treatment period.
- Annualised relapse rate up to Week 52 (ARR52) and cumulative corticosteroid dose (CCD) were highest in the group receiving placebo, whereas, they were lower in patients receiving TCZ.

- Patient Global Assessment - Visual Analog Scale (PGA-VAS) score decreased in all of the treatment groups, including placebo and there were no differences in the magnitude of decrease between the 3 TCZ exposure groups. PCS increased slightly in the TCZ exposure groups, whereas, it was unchanged in the placebo group.
- On the whole, the occurrence of serious AEs (SAEs), AEs of Infections and Infestations (II AEs), gastrointestinal (GI) AEs and neutropaenia were not correlated with TCZ exposure.
- White blood cell counts declined in all of the treatment groups, including placebo, with the largest (and a similar) decline identified in the 2 upper tertiles of TCZ exposure.
- Low density lipoprotein (LDL) cholesterol levels were unaffected by placebo, whereas, they were mildly increased in the TCZ treatment groups; however, the increases did not appear to be dependent on TCZ exposure.
- Overall, the beneficial PD effects and efficacy of TCZ improved with increasing TCZ exposure and therefore QW dosing may be more beneficial than Q2W dosing as it generally results in higher exposure in patients with GCA. In regards to safety, although there appears to be a relationship between decreased white blood cell counts and higher TCZ exposure, on the whole the incidence of AEs and abnormal laboratory parameters did not appear to be associated with increases in TCZ exposure.

Dosage selection for the pivotal studies

The sponsor's rationale for dose selection for the pivotal Phase III study in GCA patients is valid (see Attachment 2 for more details).

Efficacy

Studies providing efficacy data

The following studies provided efficacy data for the proposed indication:

- Pivotal Study WA28119: Phase III, multicentre, randomised, double blind, placebo controlled study to assess the efficacy and safety of TCZ in subjects with GCA.
- Other studies: Study ML25676 data from this study using IV TCZ was included to provide supportive evidence of efficacy/ safety of TCZ in treatment of GCA. However, the original CSR was not provided for evaluation.

Evaluator's conclusions on efficacy

Study WA28119 was a well conducted pivotal Phase III, placebo controlled (for 12 months), randomised, multicentre study in 251 patients with GCA. Majority of patients enrolled in this pivotal study were Caucasian females with 2 thirds of patients aged ≥ 65 years which represented the epidemiological profile of GCA patients in the wider population. The study included patients with both relapsing and new onset GCA disease. Furthermore, revised diagnostic criteria consistent with current clinical practice were used in order to include patients with large vessel GCA. The study was well designed with use of a stringent and clinically meaningful efficacy endpoint of sustained remission (no GCA flare) for 40 weeks and off glucocorticoids for 6 months. The use of 2 double blind, variable dose, and variable duration prednisone tapering regimens (over 26 and 52 weeks) were representative of current clinical practice. The study includes a 52 week blinded period (Part 1) followed by a 104 week open label period (Part 2), with a total

duration of 156 weeks. Clinical conduct of Part 1 of the study is complete and the Part 2 extension is currently ongoing.

The study met its primary and key secondary endpoints demonstrating that TCZ 162 mg SC QW and Q2W regimens are effective at maintaining steroid free remission in patients with GCA. Following induction and adherence to the protocol defined prednisone taper regimen, the proportion of patients in sustained remission at Week 52 was statistically and clinically significantly greater in both the QW (56%) and Q2W (53%) groups compared with the placebo (14%) group. Sensitivity analyses of the primary endpoint confirmed the robustness of the primary analysis. Non-inferiority and subsequently superiority of both TCZ regimens over placebo in combination with a 52 week prednisone taper was established with respect to the proportion of patients in sustained remission at Week 52, following induction and adherence to the protocol defined prednisone taper regimen.

Both TCZ regimens were associated with fewer GCA flares compared with placebo with the reduction in risk of flare. Average cumulative steroid doses were significantly lower in the TCZ groups compared to the placebo groups. By Week 51, only 18 to 20% of patients in both TCZ groups remained on active prednisone compared with 53 to 56% in the placebo groups. The glucocorticoid sparing effect of TCZ in Study WA28119 was both highly statistically and clinically meaningful. The median cumulative dose of prednisone at Week 52 (including all taper prednisone and escape therapy) received by the placebo (PBO) + 52 week group was more than double the cumulative doses received by the TCZ QW or Q2W groups (PBO + 52 week 3817.5 mg; TCZ QW and Q2W 1862.0 mg). Moreover, owing to the additional escape prednisone required to control disease flares, patients in the PBO + 26 week group received almost twice the cumulative glucocorticoid exposure (3296.0 mg) than either TCZ group. This reduction in steroid exposure is clinically meaningful especially due to the toxicity associated with high dose steroid exposure.

Health Related Quality of Life, assessed by Patient reported outcomes (PRO) measures (Short-Form 36 (Questionnaire) (SF-36), PG-VAS and Functional assessment of chronic illness therapy fatigue (FACIT-Fatigue)) consistently demonstrated trends towards improvement in both TCZ treatment groups.

Efficacy of TCZ 162 mg SC QW or Q2W was observed in all subgroups based on disease onset (new onset and relapsing patients), starting prednisone dose (< or > 30 mg/day), by previous history of remission, by GCA diagnosis by imaging or biopsy, by GCA diagnosis based on 1990 American College of Rheumatologists (ACR) criteria or by GCA signs and symptoms at diagnosis.

With respect to the relative efficacy of QW and Q2W SC TCZ regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW TCZ, especially in the sensitivity analysis. Moreover, consistent trends favouring QW over Q2W TCZ were seen for several additional endpoints and subgroup analyses. In both new onset and relapsing GCA patient subgroups, the difference in the proportion of patients with sustained remission was numerically higher in the TCZ QW group compared with the TCZ Q2W group and slightly more pronounced in the relapsing patient subgroup. This is especially clinically relevant as relapsing patients represents those who have already been exposed to high dose and long duration glucocorticoid regimens and present special challenges for physicians who have little choice but to re-start or to increase the dose of glucocorticoid therapy as there are currently no proven glucocorticoid sparing therapies.

Supportive evidence of efficacy was provided by the randomised, double blind, placebo controlled, Phase II Study ML25676.[35] This was the first randomised controlled trial of TCZ in 30 patients with new onset or relapsing GCA disease randomised (2:1) to receive 8 mg/kg IV TCZ every 4 weeks (Q4W) or placebo over 1 year. Results from this study showed the efficacy of TCZ in inducing remission and preventing relapse. Glucocorticoids could be rapidly tapered and discontinued by 36 weeks after the initiation of TCZ treatment.

The evidence for efficacy and safety of GCA beyond 1 year was not provided in this submission. In Study WA28119, patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open label extension phase (Part 2) of the study. GCA is usually associated with common occurrence of disease flares during glucocorticoid dose tapering or discontinuation. Therefore, it is highly likely that many patients with GCA will require treatment beyond 52 weeks in routine clinical practice. Results from the open label (OL) phase were not provided in the CSR for Study WA28119, although the sponsor's Clinical overview mentions that preliminary data from 45 patients that met the primary endpoint in Part 1 and were followed for at least an additional 48 weeks suggest that a substantial subset of GCA patients are likely to experience clinical disease flares within a year or so of stopping TCZ; the proportion of patients that previously received TCZ Q2W experienced a GCA flare (73%, 8/11) in Part 2 compared to those who previously received TCZ QW during Part 1 (33%, 8/24). Study ML25676 also showed relapse in over 50% of patients following discontinuation of TCZ (8 mg IV every 4 weeks) after a 52 week treatment course.[36] In clinical practice, some patients may be successful in sustaining disease remission off therapy, yet others may require retreatment and ongoing TCZ treatment in order to maintain disease control. The clinical evaluators feel that the choice to continue treatment beyond 52 weeks should be guided by disease activity, physician assessments, patient choice and emerging data including but not limited to long term, OL data from pivotal Study WA28119.

Safety

Studies providing safety data

The main clinical safety data for this submission was provided in the pivotal Phase III Trial WA28119 (GiACTA), which evaluated the efficacy and safety of subcutaneous (SC) TCZ treatment compared with placebo in 251 patients with GCA (clinical cut-off date 11 April 2016). Other supportive evidence was provided by the Phase II Study ML25676 which evaluated intravenous (IV) TCZ in patients with newly diagnosed or relapsing GCA).

Patient exposure

In pivotal Study WA28119 (GiACTA), primary safety analysis (Part 1) was from 250 patients treated for 52 weeks (double blind treatment period) and the long term extension (LTE) interim data (Part 2) from 88 patients who had at least 100 weeks of follow up in total. The LTE phase of Study WA28119 is currently ongoing.

Median study duration was identical (1.0 year) in all treatment groups. Based on the number of doses of SC study treatment (TCZ/ placebo) received, the patient years of exposure were similar in the TCZ Q2W and placebo groups. Given that twice as many

[35] Villiger P, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387:1921-27

[36] Adler S, et al. Termination of Tocilizumab-Treatment in Giant Cell Arteritis: Follow-up of Patients after the RCT (ClinicalTrials.gov registration number: NCT01450137). ACR/ARHP Annual Meeting 2016, Abstract number: 867, date of first publication: September 28, 2016.

patients were randomised to the TCZ QW group, the total number of patient years of exposure (86.41 patient years) was much higher than in the TCZ Q2W group (43.7 patient years), PBO + 26 week group (44.3 patient years) and PBO + 52 week group (46.0 patient years).

The median exposure to blinded SC study treatment (TCZ/placebo) was 358 days in all treatment groups. Compliance to treatment was high with median dose intensity of 100% (range of means 97.9 to 98.7%) across the treatment groups. The majority of patients in the TCZ QW group (82%), TCZ Q2W group (84%), PBO + 26 week group (86%) and PBO + 52 week group (80%) missed no more than 1 dose of blinded SC treatment during the 52 weeks of the study. Analysis of compliance to blinded SC treatment (TCZ/placebo) by study visit showed that although dose modifications were infrequent, the most common reason for non-compliance with study medication was that less than the full amount of the pre-filled syringe was administered.

Median total prednisone treatment duration was 52 weeks (1 year) in all treatment groups, accounting for open label prednisone taper, blinded prednisone/placebo as well as escape and commercial prednisone (for concomitant conditions). Median total cumulative prednisone dose was identical in the TCZ QW and TCZ Q2W groups (1862 mg). However, median total cumulative prednisone dose was higher in the PBO + 26 week (3296 mg) and PBO + 52 week (3817.5 mg) groups due to increased use of escape glucocorticoid therapy (and longer prednisone taper period in the PBO + 52 week group).

In Part 2, open label extension, 88 patients had at least 100 weeks of follow up in the study. The majority (66/88) of these patients had received TCZ either during Part 1 or Part 2 of the study. Of the 88 patients; 50 had received either TCZ QW or TCZ Q2W during Part 1 and 27 of these patients started open label TCZ during Part 2 of the study. Of the 38 patients, who were randomised to the placebo groups during Part 1, a further 16 patients received open label TCZ during Part 2 of the study As of the data cut-off date (11 April 2016), some patients had continued in Part 2 of the study up to Week 136 (scheduled visit); hence the range for duration of follow up in Part 2 ranges from 48 to 84 weeks.

In the Phase II Study ML25676, 20 patients received TCZ + prednisolone and 10 patients received placebo + prednisolone. Prednisolone was tapered to 0 mg per day at the end of the trial in 16 (80%) and 2 (20%) patients in the TCZ and placebo groups, respectively (difference 60%, 95% CI: 30, 90). The mean follow up time to stop prednisolone was 38 weeks (95% CI: 35, 42) and 50 weeks (95% CI: 46, 54), respectively (difference of 12 weeks, 95% CI: 7, 17; $p < 0.0001$). After 12 weeks, the median cumulative prednisolone dose was 34 mg/kg interquartile range (IQR 32 to 35) in the TCZ group and 36 mg/kg (IQR 34 to 39) in the placebo group; $p = 0.0477$). After 26 weeks and at the end of the trial, the median cumulative weight adapted prednisolone dose was significantly higher in the placebo group (at Week 26, 41 mg/kg (IQR 39 to 46) versus 66 mg/kg (IQR 52 to 75), respectively; $p = 0.0015$; and at Week 52, 43 mg/kg (IQR 39 to 52) versus 110 mg/kg (IQR 88 to 150) $p = 0.005$).

The LTE All-exposure RA safety dataset included data from 4171 patients with moderate to severe RA, who received at least one IV dose of TCZ in the clinical trial program and who had at least one post randomisation safety assessment providing a total of 16204.8 PY exposure. Duration of patient's participation in the study (based on the last safety information received) was summarised. This exposure (also referred to as duration in study) was used to calculate rates for AEs. Exposure to study medication (sum of actually received infusions + up to 28 days per infusion) for IV TCZ treatments (All IV TCZ Exposure RA population) was calculated. Majority of patients in the LTE All-exposure RA population were female (82%) and Caucasian (75%). Patients ranged in age from 18 to 89 years; mean (SD) age was 52.1 (12.56) years and included a variety of patient populations across the spectrum of the disease. The age of GCA patients in Study WA28119 (Part 1; mean 69.0 years across all groups; range 51 to 91 years) was older than that in the LTE

All-exposure RA population (mean 52.1 years; range 18 to 89 years) which is expected as GCA affects an older population. All other key demographic characteristics (sex, height, weight and race) were generally comparable between the 2 populations. The baseline levels of acute phase reactants were lower in Study WA28119 (Part 1 CRP: range of mean across groups 6.8 to 11.4 mg/L and ESR: range of mean across groups 20.8 to 28.8 mm/h) compared with the LTE All-exposure RA population (CRP: mean 24.4 mg/L; range 0.2 to 372 mg/L and ESR mean 46.3 mm/h; range 0 to 183 mm/h); this may have been due to fact that the patients in Study WA28119 were required to be on treatment with steroids at study entry.

Postmarketing data

Since TCZ has not yet been approved for treatment of GCA in any country at the time of this evaluation, there were no postmarketing data available for GCA. However, the following information was provided in the sponsor's Clinical Summary of Safety:

TCZ is currently approved worldwide for the treatment of RA (IV and SC formulations), polyarticular juvenile idiopathic arthritis (IV formulation) and systemic juvenile idiopathic arthritis (IV formulation). In India and Japan, TCZ has an additional indication for treatment in Castleman's disease (IV formulation). Since initial market approval in Japan for the treatment of Castleman's disease on 11 April 2005 and until the end of the reporting interval of the most recent Periodic benefit-risk evaluation reports (PBRER) (10 April 2016), TCZ has been approved for use in over 100 countries worldwide, including the EU and USA. Specifically, the SC TCZ formulation is approved in approximately 33 countries worldwide for the treatment of RA.

Since the International Birth Date (IBD) (11 April 2005) to 10 April 2016, an estimated cumulative total of 664,900 patients (522,482 PY) have received TCZ from marketing experience. The cumulative postmarketing exposure to SC TCZ is 92,216 patients (74,669 PY). Postmarketing safety data presented in the most recent PBRER 1068646 (11 October 2015 to 10 April 2016) included non-interventional studies (NIS; including post-authorisation safety studies), reports from other solicited sources and spontaneous individual case reports (that is, reports from healthcare professionals, consumers, health authorities (worldwide) and scientific literature).

Cumulatively up to 10 April 2016, a total of 154,459 events had been recorded on the Company Global Safety Database. Of these, 42,797 events were considered as SAEs. The most common AEs (≥ 10%) from postmarketing sources were within the System Organ Class (SOCs) of Infections and Infestations (16.4%); General Disorders and Administration Site Conditions (15.7%), Musculoskeletal and Connective Tissue Disorders (11.7%) and Investigations (10%).

The safety profile of SC TCZ (with the exception of ISRs, which were more common with SC TCZ) was comparable with the safety profile of IV TCZ. No new or unexpected adverse drug reactions were observed with the SC formulation.

Off label use in GCA: Cumulatively, as of 10 April 2016, there were 241 cases reported with an indication of GCA (preferred term–temporal arteritis). Of the 241 cases, 101 (41.9%) were reported from clinical studies (Studies WA28119 and ML25676). The remaining 140 cases represent off label use, of which 75 (53.6%) were reported from market research programs and patient support programs, 51 (36.4%) were spontaneous reports and 14 (10.0%) were literature reports. There is a potential for duplication of literature case reports and the individual case reports recorded on the Company Global Safety Database. Of the 140 postmarketing cases, 104 were females (74.3%), 25 (17.9%) were males and the remaining were unspecified or unknown. Of these 140 cases, 113 (80.7%) were of age ≥ 50 years, age was not reported in 26 (18.6%) and there was 1 case reported in a 29 year old. The reported cases of off label use for GCA are consistent with the known

patient demographic characteristics for this disease. The majority of these 140 postmarketing cases were reported from USA/Canada (82 (58.6%)), followed by Europe (34 (24.3%)), Switzerland (12 (8.6%)), Australia/New Zealand (6 (2.5%)), Norway (3 (2.1%)) and 1 case (0.4%) each from Brazil, Japan and Lebanon. Of these 140 postmarketing cases, there were 61 (25.3%) SAEs and 11 (7.9%) fatal events. SAEs were consistent with the observed safety profile of TCZ in other approved indications. Of the 11 fatal events, 4 were spontaneous reports, 4 were reported from NIS and 3 were from literature reports. All cases were medically confirmed and the 3 cases from literature reports were reported as causally related to TCZ. These 11 fatal events were categorised in the SOCs of Gastrointestinal Disorders, Infections and Infestations, Cardiac Disorders, General Disorders and Nervous System Disorders.

Overall, based on the data provided, no new safety concerns were identified from the post marketing data which could potentially impact the safety profile of TCZ in the proposed GCA population.

Evaluator's conclusions on safety

Treatment with TCZ was well tolerated in the 52 week double blind phase (Part 1) of Study WA28119 involving 250 adult patients with GCA. Majority of patients experienced at least one AE, with the proportion of such patients ranging between 92.2% and 98.0% across treatment groups with higher rates of AEs in the placebo groups compared with the TCZ groups: PBO + 26 week group 990.8 (95% CI: 903.2, 1084.5) AEs per 100 PY; PBO + 52 week group 1011.2 (95% CI: 923.3, 1105.3) AEs per 100 PY versus TCZ QW 872.0 (95% CI: 813.0, 934.2) AEs per 100 PY; TCZ Q2W group 948.0 (95% CI: 860.7, 1041.7) AEs per 100 PY. The incidence of SAEs (15%, 14%, 22% and 26% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively) and withdrawal due to AEs (11%, 10%, 6% and 0%, respectively) was low. No deaths were reported and no new safety signals were observed. The nature of AEs observed in the TCZ groups was similar to that in the placebo group. The most commonly reported All Grade AEs were non GCA related headache (27%, 20%, 32% and 24% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively), nasopharyngitis (29%, 25%, 18% and 26%, respectively), oedema peripheral (16%, 25%, 16% and 12%, respectively) and arthralgia (13%, 16%, 22% and 16%, respectively). Safety of QW versus Q2W was not significantly different except for a slightly higher incidence of neutropaenia and infection with QW dosing. However, there are appropriate recommendations in proposed PI to reduce the dosing to every other week in case of absolute neutrophil count (ANC) 0.5 to 1×10^9cells/L.

The nature of AEs reported in the open label LTE phase (Part 2) of Study WA28119 was generally consistent with that reported in Part 1 involving data on 88 patients on OL TCZ treatment. In both parts of the study, the highest incidence of AEs was reported in the Infections and Infestations SOC. However, the OL LTE of this study is still ongoing and should provide more long term safety data when completed.

Neutropaenia and thrombocytopaenia were the most common laboratory abnormalities observed in GCA patients treated with TCZ. The percentage of patients who experienced an National Cancer Institute Common Terminology Criteria (NCI CTC) Grade 2 low neutrophil count was 17%, 12%, 2% and 2% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively; the percentage of patients experiencing a Grade 3 neutrophil count was 4% (4 patients) in the TCZ QW group and 4% (2 patients) in the TCZ Q2W group. No patient experienced Grade 4 neutropaenia. Review of the clinical listings showed that there was no association between neutropaenia and serious infections. Thrombocytopaenia was more common in TCZ groups but majority were Grade 1 and none were associated with a bleeding event. Increased transaminases and elevated bilirubin were observed in a higher percentage of patients in the TCZ QW and TCZ Q2W

groups than in either of the placebo groups. However, there were no patients who met the laboratory criteria for Hy's law, that is, no patients in this study were identified as having a > 3 x the upper limit of normal (ULN) elevation in aspartate transaminase (AST) or alanine transaminase (ALT) and 2 x ULN in total bilirubin. Marked abnormalities in total cholesterol and LDL levels were more commonly observed in the TCZ treatment groups compared with placebo. There were no clinically relevant changes in vital signs and electrocardiogram (ECG) data was not provided.

Serious infections were reported in 7% (7/100) of patients in the TCZ QW group, 4% (2/49) of patients in the TCZ Q2W group, 4% (2/50) of patients in the PBO + 26 wk group and 12% (6/51) of patients in the PBO + 52 wk group. Opportunistic infections were reported in 2 patients in the PBO + 52 wk group and 1 patient in the TCZ Q2W group. None of these opportunistic infections led to withdrawal of the patient from study treatment. There were no reports of tuberculosis in Study WA28119. The rates of potential hypersensitivity reactions and malignancies were low and comparable between the TCZ and placebo groups. No AEs as defined by the Anaphylactic Reaction Standardised MedDRA Queries (SMQ) Narrow were reported; 2 anaphylactic AEs (eye pruritus, dyspnoea) were identified in a single patient in the TCZ Q2W group. The rate of ISRs was numerically lower in the TCZ QW group compared with the PBO + 26 week group and numerically higher in the TCZ Q2W group compared with both of the placebo groups; but with overlapping CI. Serious Bleeding, Serious Myocardial Infarction, Serious Gastrointestinal Perforation, Serious Hepatic Events, Serious Demyelinating Events were not reported in Study WA28119 (Part 1), although they have been reported in larger populations (that is, LTE All-exposure RA population and the MarketScan database).

Safety data on TCZ in treatment of GCA was also provided by the Phase II Study ML25676 (only literature reference was provided); the nature of AEs reported with IV TCZ 8 mg/kg IV every 4 weeks (which is not proposed route of administration for treatment) was generally consistent with those reported in Study WA28119 with SC TCZ.

The overall rate of AEs in the LTE All-exposure RA population (296.0 (95% CI: 293.4, 298.7) events per 100 PY) was lower than the rates observed in any arm of Study WA28119 (Part 1). The differences in AE rates between the GCA and RA populations may be attributed to the much longer exposure (16204.8 PY) and follow up (up to 5 years) in the RA population compared with the GCA population in Study WA28119 (TCZ QW = 92.9 PY and TCZ Q2W = 45.6 PY) and to the differences in background disease characteristics, patient demographics and glucocorticoid toxicity in the placebo groups in GCA (Study WA28119; Part 1). In general, the rates of AEs were highest in the initial 6 months in Study WA28119 (Part 1) and the LTE All-exposure RA population. Overall, the safety profile observed with SC TCZ in GCA in Study WA28119 (Part 1) was generally consistent with the established safety profile of IV TCZ in RA (except ISRs; known to be associated with SC administration and not IV). No new signals were observed in the pivotal Study WA28119.

The sponsor also conducted a real world data study in order to further characterise the longer term risk associated with the use of glucocorticoids in GCA which provided evidence of a significant increase in the risk for a glucocorticoid related AE with each 1 g increase in cumulative glucocorticoid dose. Moreover, each cumulative gram was also associated with a significant increase in risk for an adverse event of special interest (AESI). This may be clinically relevant especially in light of the glucocorticoid sparing elicited by TCZ in Study WA28119, but also when considered against the observation that patients in real world clinical practice are exposed to considerably higher cumulative glucocorticoid doses than those in the Study WA28119 control groups.

Overall, the safety profile of SC TCZ in patients with GCA observed in Study WA28119 is generally consistent with that reported in the investigator initiated Trial ML25676 in GCA

with IV TCZ, the individual case reports for GCA reported in literature and with the established safety profile of IV TCZ in RA.

First Round Benefit-Risk Assessment

First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Pivotal study had good study design and was well conducted involving 250 patients with active GCA. Efficacy endpoints evaluated (continuous remission and discontinuation of glucocorticoids) are valid and clinically relevant for GCA. Statistically and clinically significant treatment benefit of proposed dose of TCZ 162 mg once weekly by SC administration combined with a 26 week glucocorticoid regimen in comparison to both a short 26 weeks schedule and a longer 52 weeks schedule in terms of sustained remission at 52 weeks. Robustness of primary efficacy results confirmed in a number of sensitivity analyses designed to control for various features of the composite primary and key secondary efficacy endpoints. Reduction in risk of GCA flares in both TCZ groups compared to placebo groups. A significant glucocorticoid sparing effect of TCZ was shown. A lower proportion of patients in the TCZ treatment groups remained on active prednisone to Week 52 compared with the placebo groups. Mean annualised GCA relapse rate (which accounts for multiple flares in one patient) was lowest in the TCZ QW group. Efficacy demonstrated in all subgroup analyses. Health Related Quality of Life, assessed by PRO measures (SF-36, patient's global assessment VAS and FACIT-Fatigue) consistently demonstrated trends towards improvement in both TCZ treatment groups. With respect to the relative efficacy of QW and Q2W SC TCZ regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW TCZ. Moreover, consistent trends favouring QW over Q2W TCZ were seen for several additional endpoints and subgroup analyses. There were no new safety signals related to TCZ treatment. The profiles of both AEs and AESIs	Sustained remission rates at Week 52 were 56%, 53%, 14% and 17.6% in the TCZ QW + 26 week taper, TCZ Q2W + 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups, respectively. Proportion of patients experiencing GCA flares was 23.0%, 26.5%, 68% and 49% in the TC QW + 26 wk taper, TCZ Q2W+ 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups, respectively. The median cumulative dose of prednisone at Week 52 (including all taper prednisone and escape therapy) received by the PBO + 52 week (3817.5 mg) and PBO + 26 week group (3296.0 mg) was double the cumulative doses received by the TCZ QW or Q2W groups (1862.0 mg). By Week 51 glucocorticoids were being received by 18/100 (18%) of patients in the TCZ QW group and 10/49 (20%) of patients in the TCZ Q2W group compared with 28/50 (56%) of patients in the PBO + 26 wk group and 27/51 (53%) of patients in the PBO + 52 week group. Relapse rates were 0.41/year, 0.67/year, 1.74/year and 1.30/year in the TC QW + 26 week taper, TCZ Q2W+ 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups, respectively. Efficacy of TCZ 162 mg SC every week (QW) or every 2 weeks (Q2W) was observed in all subgroups based on disease onset (new onset and relapsing patients), starting prednisone dose (≤ or > 30 mg/day), by previous history of remission, by GCA diagnosis by imaging or biopsy, by GCA diagnosis based on 1990 ACR criteria or by GCA signs and symptoms at diagnosis. However, details of actual sustained remission rates at Week 52 in new onset and relapsing GCA patients was not provided. Although differences between the QW and Q2W TCZ groups were minor, there is evidence to suggest that higher exposures to TCZ following once weekly dosing regimen may

Indication	
Benefits	**Strengths and Uncertainties**
were balanced across the TCZ and placebo treated groups, in agreement with the well characterised safety profile of TCZ in other indications.	potentially reduce incidence of relapse. No safety concerns were identified with more frequent QW dosing compared with the Q2W dosing with exception of increased risk of neutropaenia. However, the proposed PI has adequate recommendations for reducing dose to every other week in patients who develop neutropaenia with ANC 0.5 to 1 x 10^9 cells/L. No data on long term safety beyond 52 weeks.

First round assessment of risks

Risks	Strengths and Uncertainties
Limited evidence of efficacy and safety beyond 52 weeks. Risk of relapse following discontinuation of TCZ treatment after 52 weeks in the pivotal Study WA28119. Risk of serious infections, opportunistic infections and malignancies. Risk of neutropaenia and thrombocytopaenia. Risk of injection site reactions and hypersensitivity. Development of ADA antibodies.	Results from the ongoing pivotal Study WA28119 should provide data related to long term efficacy and safety of TCZ in treatment of GCA. This has not been evaluated adequately although it appears that risk of relapse is lesser following QW dosing compared to Q2W dosing. Serious infections reported in 7%, 4%, 4% and 12% in the TC QW + 26 week taper, TCZ Q2W+ 26 week taper, placebo + 26 week taper and placebo + 52 week taper groups, respectively. Opportunistic infections were reported in 2 patients in the PBO + 52 week group and 1 patient in the TCZ Q2W group. None of these opportunistic infections led to withdrawal of the patient from study treatment. No reports of tuberculosis. The percentage of patients who experienced an NCI CTC Grade 2 low neutrophil count was 17%, 12%, 2% and 2% in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively; Grade 3 neutropaenia 4%, 4% and 0%, 0%, respectively. No patient experienced Grade 4 neutropaenia. No association between neutropaenia and serious infections. Majority of thrombocytopaenia AEs were Grade 1; none of these events were associated with serious bleeding. Low incidence and no ISR reported as a SAE or required withdrawal from treatment. Only 1.1 to 6.5% of patients overall developed treatment induced ADA. None experienced any anaphylaxis, serious / clinically significant hypersensitivity reactions, ISRs, or withdrew due to lack of efficacy.

First round assessment of benefit-risk balance

GCA is a potentially life threatening condition associated with substantial impairment of the day to day functioning of patients. There are currently no approved therapies specifically for GCA. The cornerstone of treatment is high dose glucocorticoids followed by long term steroid tapering. Patients often experience steroid related adverse events (AEs) due to the toxic burden of long term, high dose steroid treatment. Prompt diagnosis and rapid initiation of treatment for GCA are critical to prevent blindness and other ischaemic complications.[37] Elevated tissue and serum levels of IL-6 have been reported in the pathogenesis of GCA and correlate with disease activity. Thus, inhibition of the biological activity of IL-6 or its receptor represents a promising new approach for the treatment of GCA. Tocilizumab is a recombinant humanised, anti-human monoclonal antibody of the IgG1 subclass. The molecule targets both the soluble and membrane bound forms of the IL-6 receptor (sIL-6R and mIL-6R), adhering to the IL-6 binding site of these receptors and inhibiting IL-6 signalling in a competitive manner.

The primary and key secondary efficacy endpoints were met in the well designed and conducted, pivotal Phase III Study WA28119 (GiACTA) that investigated the safety and efficacy of TCZ in 250 adult patients with active GCA. Treatment with TCZ SC 162 mg given every week or every other week along with a 26 week prednisone taper regimen produced sustained remission rates of 53 to 56% in the TCZ treatment groups compared with 14 to 17% in the placebo groups. These effects were observed in patients with new onset or relapsing disease. Primary efficacy results were supported by reduction in incidence of GCA flares and reduction in cumulative glucocorticoid dose. This reduction in steroid exposure is considered to be clinically meaningful with respect to decreasing the toxicity burden of high dose steroid exposure.

With respect to the relative efficacy of QW and Q2W SC TCZ regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW TCZ. Moreover, consistent trends favouring QW over Q2W TCZ were seen for several additional endpoints and subgroup analyses. Although differences between the QW and Q2W TCZ groups were minor, there is evidence to suggest that higher exposures to TCZ following once weekly dosing regimen may potentially reduce incidence of relapse although this needs to be confirmed. The proposed weekly dosing with TCZ for treatment of GCA was also supported by PK-PD results. TCZ exposure was considerably higher (approximately 5.5 fold) following administration QW compared Q2W. Although, the logistic regression did not indicate a significant relationship between exposure and probability of REMI52, the risk of GCA flare appeared to be reduced in patients with higher exposure of TCZ; in the TCZ QW, the risk of flare was reduced by 40% and 55% for patients at the 5th and 95th exposure percentile, respectively. By contrast, for the Q2W TCZ treatment arm, risk of flare was increased by 44% for patients at 5th percentile whereas, at the 95th percentile of exposure flare risk was reduced by 46%. The ARR52 and the CCD also showed numerical advantages with higher TCZ exposure.

No new safety signals were observed in the study. The AEs reported were comparable between the TCZ and placebo arms and were consistent with the current TCZ profile in other indications. TCZ treatment was also associated with a clinically significant reduction in the use of steroids even within a follow up period of only 52 weeks. No safety concerns were identified with more frequent QW dosing compared with the Q2W dosing with exception of increased risk of neutropaenia. However, the proposed PI has adequate recommendations for reducing dose to every other week in patients who develop neutropaenia with ANC 0.5 to $1x10^9$ cells/L. Although there appears to be a PK-PD relationship between decreased white blood cell counts and higher TCZ exposure, on the

[37] Matteson EL, Buttgereit F, Dejaco C, et al. Glucocorticoids for Management of Polymyalgia Rheumatica and Giant Cell Arteritis. Rheum Dis Clin N Am. 2016;42:75-90.

whole the incidence of AEs, SAEs, AEs of Infections and Infestations (II AEs) and gastrointestinal AEs (GI AEs) were not correlated with TCZ exposure.

The evidence for efficacy and safety of GCA beyond 1 year was not provided in this submission. In Study WA28119, patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open label extension phase (Part 2) of the study. GCA is usually associated with common occurrence of disease flares during glucocorticoid dose tapering or discontinuation Therefore, it is highly likely that many patients with GCA will require treatment beyond 52 weeks in routine clinical practice. The clinical evaluators feel that the choice to continue treatment beyond 52 weeks should be guided by disease activity, physician assessments, patient choice and emerging data including but not limited to long term, OL data from pivotal Study WA28119.

Currently, the only treatment option for GCA is limited to glucocorticoids which are associated with significant toxicity especially following long term use. Considering the clear and long standing unmet treatment need in GCA, the valid rationale to target IL-6, the manageable TCZ safety profile and compelling evidence of efficacy in the pivotal Phase III Study WA28119, TCZ given once weekly by SC administration along with prednisone tapering provides a viable treatment option for treatment of adults with active GCA.

Overall, the benefit-risk balance of TCZ treatment in GCA is considered favourable.

First Round Recommendation Regarding Authorisation

Approval of Actemra (Tocilizumab 162 mg SC once weekly) is recommended for treatment of giant cell arteritis (GCA) in adult patients.

The approval is subject to the following:

- Incorporation of suggested changes to proposed Australian PI specifically inclusion of word ‘active GCA’ to reflect the patient population evaluated in the pivotal study.
- Satisfactory response to Clinical questions (see Attachment 2).
- Provision of data from ongoing OL LTE phase of Study WA29119 when it is completed.

Second Round Evaluation of clinical data submitted in response to questions

For details of the clinical questions raised, the sponsor’s responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Actemra in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Actemra in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of benefit-risk balance

The benefit risk balance of Actemra for treatment of GCA is favourable.

Second round recommendation regarding authorisation

Approval of Actemra (Tocilizumab 162 mg SC once weekly) is recommended for treatment of giant cell arteritis (GCA) in adult patients.

The approval is subject to the following:

- incorporation of suggested changes to proposed Australian PI; and
- assurance that sponsors will provide data from ongoing OL-LTE phase of Study WA29119 when it is completed (expected to complete in the first quarter of 2019).

VI. Pharmacovigilance findings

Risk management plan

- In support of the extended indication, the sponsor has submitted EU-RMP version 21.0; dated 11 November 2016; DLP October 2016, and ASA version 6.0 dated November 2016. The most recently evaluated EU-RMP was version 16.3 dated December 2014 and ASA version 4.0 dated 9 February 2015.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 4: Summary of ongoing safety concerns

R = routine; A = additional.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Serious infection	✓[1]	✓[2,3,4]	✓	–
	Complications of diverticulitis	✓[1]	✓[2,3,4]	✓	–
	Serious hypersensitivity reactions	✓[1]	✓[2,3,4]	✓	✓[5,6,7,8]
	Neutropaenia	✓[1]	✓[2,3,4]	✓	–
Important potential risks	Thrombocytopaenia and the potential risk of bleeding	✓[1]	✓[2,3,4]	✓	–
	Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity	✓[1]	✓[2,3,4]	✓	–
	Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events	✓[1]	✓[2,3,4]	✓	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Malignancies	✓1	✓2,3,4	✓	–
	Demyelinating disorders	✓1	✓2,3,4	✓	–
	Immunogenicity	✓	✓2	✓	–
Missing information	Elderly Patients	✓	✓2,3,4	✓	–
	Paediatric patients	✓	✓2,3	✓	–
	Effects during pregnancy	✓	✓2,3	✓	–
	Hepatic impairment	✓	–	✓	–
	Renal impairment	✓	–	✓	–
	Combination with biologics	✓	✓3,4	✓	–
	Safety in patients <60 kg in switcher population	✓	✓3	–	–
	Long term safety in patients in the switcher patient population	✓	✓3	–	–
Identified and potential interactions including food-drug and drug-drug interactions	CYP450 enzyme normalization	✓	✓2	✓	–

1) Guided questionnaire; 2) Clinical trial; 3) Patient registries 4) US healthcare claims database;
5) Anaphylaxis flowchart 6) CTiv infusion management program; 7) Healthcare professional brochure;
8) Patient brochure.

- Ongoing additional pharmacovigilance activities have been proposed to monitor relevant safety concerns. These activities have been accepted in the previous evaluation.
- Ongoing additional risk minimisation has been proposed to monitor the risk of serious hypersensitivity reactions. This has been accepted by the previous evaluation.

Recommendations at the second round

There remain outstanding recommendations:

1. The provided follow up forms are considered fit for purpose to characterise the specific safety concerns. However, the forms require modification to collect appropriate patient ethnicity demographic categories for Australian use. The Australian Indigenous identity status (Aboriginal and Torres Strait Islander, ATSI) should be recorded as one of the following options: 'Aboriginal', 'Aboriginal and Torres Strait Islander', 'Torres Strait Islander', or 'neither'.

2. The proposed Consumer Medicine Information (CMI) contains detailed instructions, including graphics, to guide patients with self-injection. This information is not available in the PI. The sponsor should advise whether the 'Actemra for me' patient guide, which contains instructions for administration, is still actively distributed, and provide recent distribution metrics demonstrating that patients initiated on Actemra for self-injection receive this information. If this guide is not being provided to patients initiated on Actemra, then the RMP evaluator considers that the sponsor should provide the CMI in the packaging in addition to the PI so that patients have an immediately available reference to support correct self-injection technique.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement EU-RMP (version 21.0, date 11 November 2016, data lock point October 2016) with Australian Specific Annex (version 6.0, date November 2016) and any future updates as a condition of registration.

Other advice for the Delegate

The Delegate's attention is drawn to the CMI recommendation as it remains the view of the RMP evaluator that the CMI (or appropriate Instructions for Use (IFU)) be included in the packaging to promote safe use in home treatment with Actemra

VII. Overall conclusion and risk/benefit assessment

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

Quality

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

Nonclinical

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

Clinical

The clinical evaluator recommends approval of the new indication subject to incorporation of recommended changes to the PI and an assurance to submit the data from the long term extension phase of Study WA28119 when completed.

Pharmacokinetics

The bioavailability of the SC formulation of TCZ has been previously reported to be 0.8. Estimated T_{max} is 3 days and central and peripheral volumes of distribution 4.09 L and 3.37 L respectively. Elimination comprises linear and non-linear clearance, so $t_{1/2}$ is

concentration dependent. $t_{1/2}$ at steady state was between 18.3 to 18.9 days for 162 mg SC QW regimen.

The proposed weekly dosing with SC TCZ is supported by the PK data from Study WA28119, a Phase III, multicentre, randomised, double blind, placebo controlled study of GCA patients. This study assessed the PK of TCZ following 162 mg doses of SC TCZ weekly (QW) or every other week (Q2W) in combination with a 26 week prednisone taper regimen in patients with GCA. At Week 52 following Q2W dosing, mean exposure to TCZ was approximately 5.5 fold lower than following QW dosing (mean TCZ concentrations were 67.93 ± 34.40 µg/mL and 12.22 ± 10.02 µg/mL for the TCZ QW and TCZ Q2W groups, respectively). The PopPK study also predicted that TCZ exposure was lower following Q2W dosing.

Pharmacodynamics

TCZ binds specifically to both soluble and membrane bound IL-6 receptors and has been shown to inhibit sIL-6R and mIL-6R mediated signalling.

The beneficial PD effects of TCZ improved with increasing TCZ exposure, suggesting that QW dosing may be more beneficial than Q2W dosing.

Dosage selection for the pivotal Phase III study, 162 mg SC QW or Q2W, was derived from experience with TCZ in adult RA. The SC route of administration was selected because it is more convenient for the older patient population with GCA.

Efficacy

The pivotal efficacy and safety study is Study WA28119, a Phase III, multicentre, randomised, 4 arm, double blind, and placebo controlled study involving 251 patients with GCA. The study included a 52 week blinded period (Part 1) followed by a 104 week open label period (Part 2). The majority of patients in the study were Caucasian (96.8%. The majority were female (74.9%) and the mean age was 69 years. 2 thirds were aged ≥ 65 years. The study population included adult patients with GCA who had active disease within the 6 weeks prior to the baseline visit. The study included patients with new onset (47%) and relapsing (53%) GCA. Diagnosis of GCA was based on age ≥ 50 years, history of ESR ≥ 50 mm/hour and at least one of the following:

- unequivocal cranial symptoms of GCA (new onset localised headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischaemia related vision loss, or unexplained mouth or jaw pain upon mastication);
- symptoms of polymyalgia rheumatic (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness; and
- at least one of the following:
  - temporal artery biopsy revealing features of GCA
  - evidence of large vessel vasculitis by angiography or cross sectional imaging study such as MRA, CTA, or PET-CT.

The study exclusion criteria were clinically reasonable.

Patients were randomly assigned in a 2:1:1:1 ratio to one of 4 treatment arms:

1. Weekly SC TCZ 162 mg in combination with a 26 week prednisone taper
2. Every other week SC TCZ 162 mg in combination with a 26 week prednisone taper
3. Weekly SC placebo in combination with a 26 week prednisone taper
4. Weekly SC placebo in combination with a 52 week prednisone taper

Patients and caregivers were trained to perform the SC injections from the initial treatment. After the first 2 injections, once the patient or the patient's caregiver had demonstrated competence in giving the injection correctly, SC injections could be administered by the patient or the patient's caregiver at the site. Once the patient or the caregiver had demonstrated competence in giving the injection after the first 4 visits, SC injections could be administered at home. If a patient was unable or did not wish to administer the study drug at home, clinic staff could administer the injections to the patient.

The primary objective was to evaluate the efficacy of TCZ compared to placebo, in combination with a 26 week prednisone taper regimen, as measured by the proportion of patients in sustained remission at Week 52. Remission was defined as the absence of flare and normalisation of the CRP (< 1 mg/dL). To be considered for sustained remission of GCA, induction of remission had to occur within 12 weeks of Baseline. Sustained remission was defined as absence of flare following induction of remission up to the 52 week time point.

The study met its primary endpoint. Both TCZ dosage regimens demonstrated clinical and statistical superiority over placebo. At Week 52, sustained remission was achieved in 56.0%, 53.1% and 14% of patients in the TCZ QW, TCZ Q2W and placebo + 26 week taper groups, respectively; the difference in the percentage of responders between the TCZ QW group and placebo was 42.0% (99.5% CI: 18.0 to 66.0, p < 0.0001) and that between the TCZ Q2W group and placebo was 39.1% (99.5% CI: 12.5 to 65.7, p < 0.0001).

Table 5: Proportion of patients achieving sustained remission at Week 52 (ITT population)

	PBO QW + 26 Week Prednisone Taper N = 50	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
Responders [a]	7 (14.0%)	56 (56.0%)	26 (53.1%)
Non-Responders [b, c]	43 (86.0%)	44 (44.0%)	23 (46.9%)
Unadjusted difference in response rates		42.00	39.06
99.5% CI		(18.00, 66.00)	(12.46, 65.66)
p-value (Cochran-Mantel-Haenszel) [d, e, f]		< 0.0001	< 0.0001

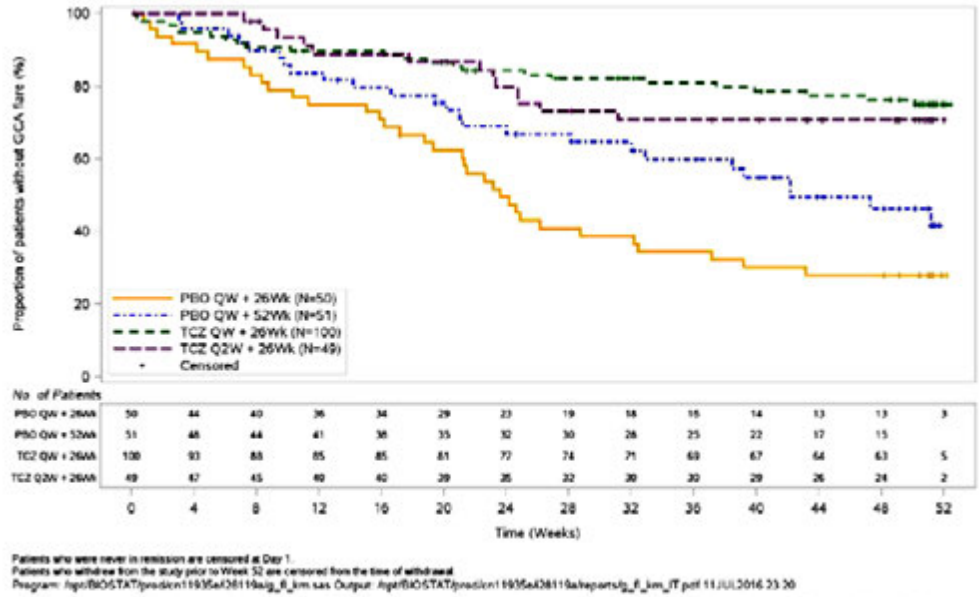
Patients were in sustained remission when they were responders from Week 12 to Week 52.
Elevated ESR attributed to GCA was reflected in flare by the investigator.
Patients who had received > 100 mg additional glucocorticoid dosing from Week 12 to Week 52 were considered as not having adhered to the protocol-defined prednisone taper regimen.
[a] Patients in remission were classed as responders.
[b] Patients with elevated CRP whose next CRP value was elevated or missing were classed as non-responders.
[c] Patients not adhering to the protocol-defined prednisone taper were classed as non-responders.
[d] Superiority comparison uses pooled SE.
[e] Stratification factor, starting prednisone dose (≤ 30 mg/day, >30 mg/day) was included in the model.
[f] Analysis adjusted for the randomization stratification factor applied at baseline.
Source: t_ef_sum_IT

The key secondary objective was to evaluate the efficacy of TCZ + 26 week prednisone taper versus placebo + 52 week prednisone taper, as measured by the proportion of patients in sustained remission at Week 52. Both TCZ dosage regimens demonstrated superiority over placebo + 52 week taper, so this secondary endpoint was met. The proportion of patients in sustained remission at Week 52 was 56% for TCZ QW (p < 0.0001) and 53.1% for TCZ Q2W (p = 0.0002) compared with 17.6% for the placebo + 52 week taper group.

Other secondary endpoints included the efficacy of TCZ in combination with a 26 week prednisone taper regimen versus both placebo groups, as measured by the following: time to GCA disease flare after clinical remission, cumulative corticosteroid dose, effect on patient's quality of life, and PK and PD of TCZ in patients with GCA. The proportion of

patients with GCA flare was 69%, 49%, 23% and 26.5% in the placebo + 26 week taper, placebo + 52 week taper, TCZ QW + 26 week taper and TCZ Q2W + 26 week taper groups, respectively. Time to event analysis showed a statistically significantly lower risk of GCA disease flare in both TCZ dose groups compared to the placebo + 26 week taper group: hazard ratios (HRs) were 0.23 (99% CI: 0.11 to 0.46; p < 0.0001) for the TCZ QW group and 0.28 (99% CI: 0.12 to 0.66; p < 0.0001) for the TCZ Q2W group. Comparison with the placebo + 52 week taper group showed a statistically significant lower risk of GCA flare in the TCZ QW group but the numerical improvement in the TCZ Q2W group did not reach the pre-specified threshold for statistical significance.

Figure 1: Kaplan Meier plot of time to first GCA flare (ITT population)



Note: the low number of patients at risk at Week 52 is due to the method used to calculate the Week 52 time window. The majority of patients completed their Week 52 visit in the few days prior to the end of the window and are therefore censored at the very end of the Week 52 window. This does not impact the results in any way and is applied consistently across all patients and groups.

Health Related Quality of Life, assessed by patient reported outcome measures (SF-36, patient's global Visual Analogue Scale and FACIT-Fatigue) showed consistent trends towards improvement in both TCZ treatment groups.

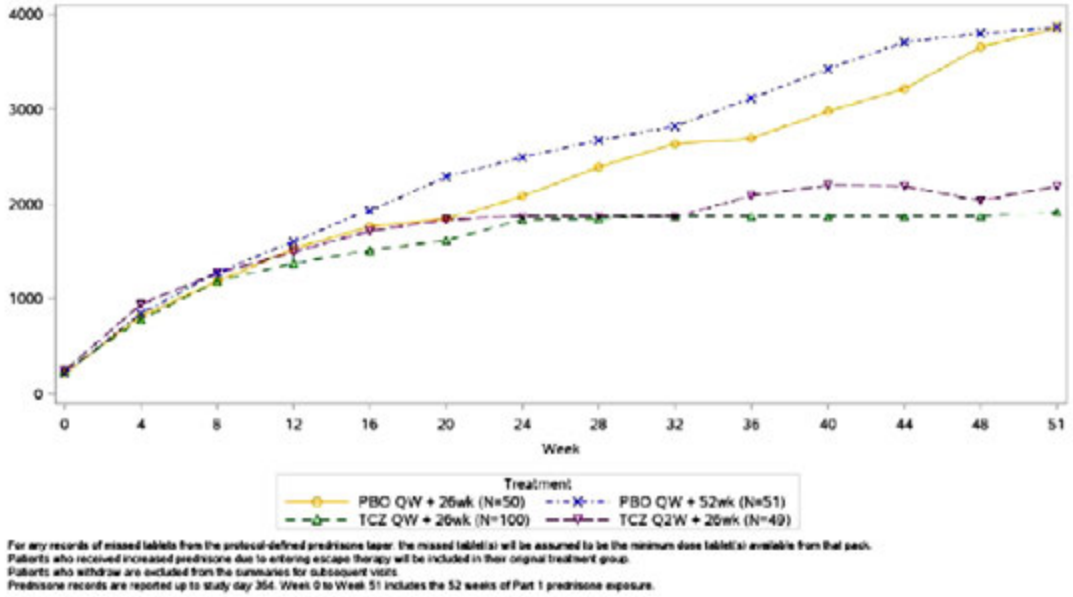
The cumulative prednisone dose to Week 52 was statistically significantly lower in both the TCZ QW and TCZ Q2W treatment groups when compared to placebo + 26 or 52 week taper. The median cumulative dose of prednisone at Week 52 (including all taper prednisone and escape therapy) for the placebo + 52 week taper group (3817.5 mg) was more than double the cumulative doses for the TCZ QW or Q2W groups (1862.0 mg, p < 0.0001). The median cumulative dose of prednisone at Week 52 for the placebo + 26 week taper group was 3296.0 mg. In the TCZ groups, there was little increase in the cumulative prednisone dose after the 26 week taper period.

Table 6: Summary of cumulative prednisone dose to Week 52 (ITT population)

Statistics	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
Expected Cumulative Dose (mg)				
n	50	51	100	49
Mean	1522.78	2694.52	1500.80	1606.93
Median	1337.00	2607.50	1337.00	1442.00
SD	540.10	732.88	567.78	571.83
Min - Max	952.0 - 2632.0	822.5 - 3902.5	350.0 - 2632.0	332.5 - 2632.0
Actual Cumulative Dose (mg)				
n	50	51	100	49
Mean	3765.19	4199.00	2097.84	2447.00
Median	3296.00	3817.50	1862.00	1862.00
SD	2022.45	2291.32	1248.45	1827.31
Min - Max	932.0 - 9777.5	822.5 - 10697.5	630.0 - 6602.5	295.0 - 9912.5
95% CI of the Median	(2729.5, 4023.5)	(2817.5, 4425.5)	(1582.0, 1942.0)	(1568.0, 2239.5)
P-Value				
PBO QW + 26 Week Prednisone Taper		0.8297	<.0001	0.0003
PBO QW + 52 Week Prednisone Taper			<.0001	<.0001

Van Elteren's test was used to calculate p-values. Analysis was stratified by starting prednisone dose (<=30mg/day, >30mg/day). For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) will be assumed to be the minimum dose tablet(s) available from that pack. Patients who received increased prednisone due to entering escape therapy will be included in their original treatment group. Expected cumulative dose is based on a patient's starting prednisone dose in the taper and assumes they continued the taper without error. Actual cumulative dose is based on actual records of prednisone taken and includes all escape therapy and commercial prednisone as well as taper prednisone

Figure 2: Plot of median cumulative prednisone dose by visit and treatment group to Week 52 (ITT population)



For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) will be assumed to be the minimum dose tablet(s) available from that pack.
Patients who received increased prednisone due to entering escape therapy will be included in their original treatment group.
Patients who withdraw are excluded from the summaries for subsequent visits.
Prednisone records are reported up to study day 364. Week 0 to Week 51 includes the 52 weeks of Part 1 prednisone exposure.

Efficacy of TCZ was demonstrated in all subgroup analyses, including disease onset (new onset versus relapsing), starting prednisone dose, previous history of remission, diagnosis by imaging or biopsy, diagnosis based on 1990 ACR criteria, and signs and symptoms at time of diagnosis.

Table 7: Patients achieving sustained remission at Week 52 by disease onset status

	PBO QW + 26 Week Prednisone Taper (N=50)	PBO QW + 52 Week Prednisone Taper (N=51)	TCZ QW + 26 Week Prednisone Taper (N=100)	TCZ Q2W + 26 Week Prednisone Taper (N=49)
New Onset Patients				
n	23	23	47	26
Sustained remission	5 (21.7%)	5 (21.7%)	28 (59.6%)	15 (57.7%)
Not sustained remission	18 (78.3%)	18 (78.3%)	19 (40.4%)	11 (42.3%)
Relapsing Patients				
n	27	28	53	23
Sustained remission	2 (7.4%)	4 (14.3%)	28 (52.8%)	11 (47.8%)
Not sustained remission	25 (92.6%)	24 (85.7%)	25 (47.2%)	12 (52.2%)

Patients in remission will be classed as responders.
Patients are in sustained remission when they are responders from Week 12 to Week 52.
Patients who have elevated CRP and their next CRP value is elevated or missing will be classed as non-responders.
Elevated ESR which attribute to GCA is reflected in Flare by investigator.
Patients who Flare, move to Escape medication or withdrawn prior to week 52 will be classed as non-responders.
Patients who did not adhere to the protocol-defined prednisone taper will be classed as non-responders.
Patients who have received more than 100mg additional CS dosing from Week 12 to Week 52 are considered as not adhered to the protocol-defined prednisone taper regimen.
Percentages are based on n.

Table 8: Cumulative Glucocorticoid Dose by Disease Status at Baseline (ITT Population)

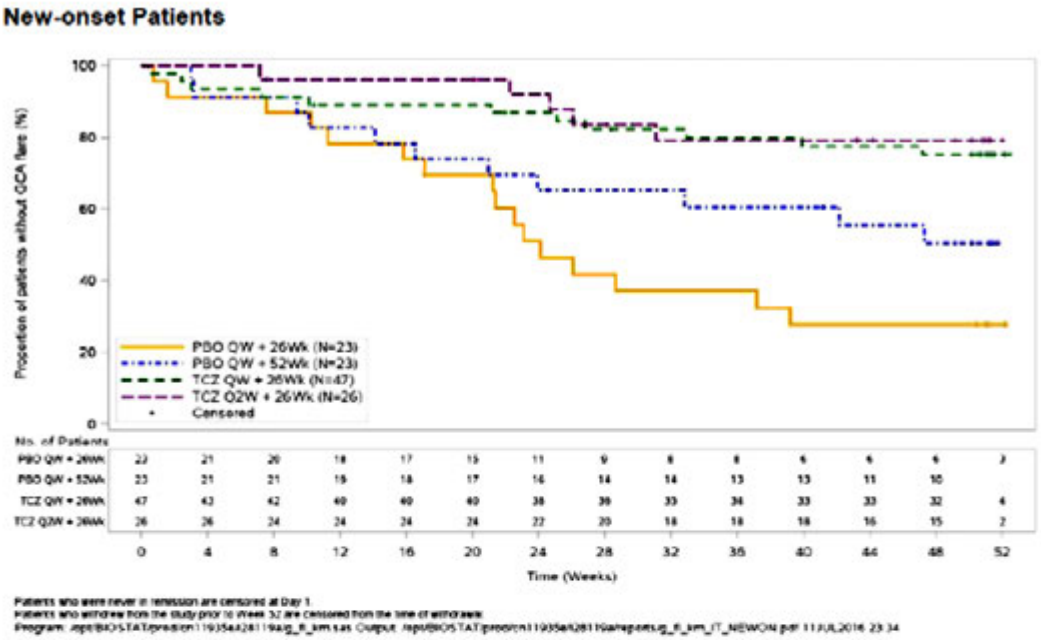
	PBO QW + 26 Week Prednisone Taper N = 50	PBO QW + 52 Week Prednisone Taper N = 51	TCZ QW + 26 Week Prednisone Taper N = 100	TCZ Q2W + 26 Week Prednisone Taper N = 49
New-onset (n)	23	23	47	26
Mean	3632.11	4136.83	2406.67	2712.29
SD	2212.91	2055.62	1341.88	1850.21
Median (mg)	3068.00	3817.50	1942.00	2202.00
min-max	1125.0 - 9777.5	2017.5 - 10275.0	630.0 – 6602.5	982.0 – 9912.5
95% CI	(2262.0, 4289.0)	(2577.5, 4584.5)	(1822.0, 2519.0)	(1815.5, 3079.0)
Relapsing (n)	27	28	53	23
Mean	3878.56	4250.06	1823.96	2147.11
SD	1880.44	2504.68	1100.85	1793.86
Median (mg)	3860.50	3785.50	1385.00	1568.00
min-max	932 – 8043.5	822.5 – 10697.5	658.0 – 5912.0	295.0 – 8410.0
95% CI	(2678.0, 5116.5)	(2222.5, 5372.5)	(1127.0, 1862.0)	(1114.5, 2239.5)

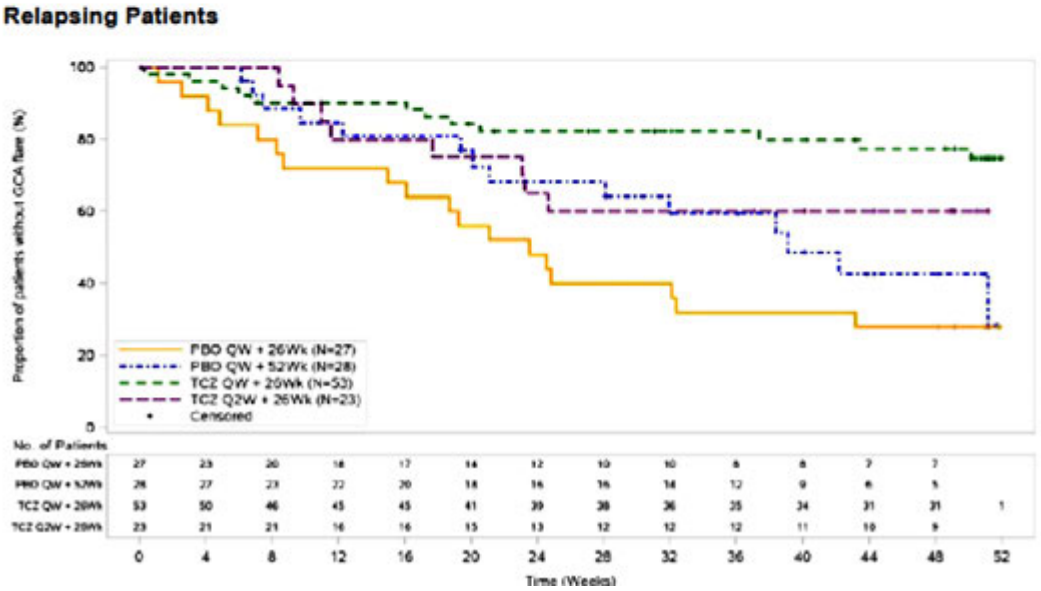
Van Elteren's test was used to calculate p-values. Analysis was stratified by starting prednisone dose (≤ 30mg/day, >30mg/day).

For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) were assumed to be the minimum dose tablet(s) available from that pack. Patients who received increased prednisone due to entering escape therapy were included in their original treatment group.

Actual cumulative dose is based on actual records of prednisone taken and includes all escape therapy and commercial prednisone as well as taper prednisone.

Figure 3: Kaplan-Meier plot of time to first GCA disease flare by disease status at Baseline (ITT population)





The pivotal study demonstrated superiority of QW and Q2W dosing over placebo. With regard to the relative efficacy of QW and Q2W regimens, small differences were seen in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW TCZ, especially in the sensitivity analysis. Consistent trends favouring QW over Q2W TCZ were seen for other endpoints and subgroup analyses. The difference in the proportion of patients with sustained remission was numerically higher in the TCZ QW group compared with the TCZ Q2W group for both new onset and relapsing GCA subgroups. The difference was slightly more pronounced in the relapsing patient subgroup. The clinical relevance of this is that patients with relapsing GCA have already been exposed to prolonged, high dose glucocorticoid therapy and currently have little choice but to increase the steroid dose/duration. The QW group had a numerically lower cumulative glucocorticoid dose than the Q2W group at Week 52 in both new onset and relapsing patients.

The following information regarding preliminary results from the extension study was provided in the sponsor's Clinical overview but could not be confirmed by the clinical evaluators:

'*Patients in remission at Week 52 stopped their TCZ injections and are being followed up off TCZ during the open label extension phase (Part 2) of the study. Preliminary data from 45 patients that met the primary endpoint in Part 1 and were followed for at least an additional 48 weeks revealed that a higher proportion of patients that previously received TCZ Q2W experienced a GCA flare (73%, 8/11) in Part 2 compared to those who previously received TCZ QW during Part 1 (33%, 8/24). This is consistent with the concept that the TCZ QW regimen may be more effective at suppressing disease activity than the TCZ Q2W dose.*'

Supportive evidence of the efficacy of TCZ (8 mg IV every 4 weeks for 1 year) in inducing remission and preventing relapse of GCA was provided in the literature reference for the randomised, double blind, placebo controlled, Phase II Study ML25676.

Safety

Study WA28119 was the pivotal safety study. Treatment with TCZ was well tolerated in the 52 week double blind phase (Part 1) involving 250 adult patients with GCA. The majority of patients experienced at least one AE, with the proportion of such patients ranging between 92.2% and 98.0% across treatment groups with higher rates of AEs in the placebo groups compared with the TCZ groups. The incidence of SAEs (15%, 14%, 22% and 26% in the TCZ QW, TCZ Q2W, placebo + 26 week and placebo + 52 week groups, respectively) and withdrawal due to AEs (11%, 10%, 6% and 0%, respectively) was low. No deaths were reported and no new safety signals were observed. The nature of AEs observed in the TCZ groups was similar to that in the placebo group. The most commonly reported All Grade AEs were non GCA related headache (27%, 20%, 32% and 24% of patients in the TCZ QW, TCZ Q2W, PBO + 26 week and PBO + 52 week groups, respectively), nasopharyngitis (29%, 25%, 18% and 26%, respectively), oedema peripheral (16%, 25%, 16% and 12%, respectively) and arthralgia (13%, 16%, 22% and 16%, respectively).

Serious infections were reported in 7% (7/100) of patients in the TCZ QW group, 4% (2/49) of patients in the TCZ Q2W group, 4% (2/50) of patients in the PBO + 26 week group and 12% (6/51) of patients in the PBO + 52 week group. Opportunistic infections were reported in 2 patients in the PBO + 52 week group and 1 patient in the TCZ Q2W group. None of these opportunistic infections led to withdrawal of the patient from study treatment. There were no reports of tuberculosis. The rate of infection/serious infection events was 200.2/9.7 events per 100 patient years in the Actemra weekly group and 160.2/4.4 events per 100 patient years in the Actemra every other week group as compared to 156.0/4.2 events per 100 patient years in the placebo + 26 week prednisone taper and 210.2/12.5 events per 100 patient years in the placebo + 52 week taper groups.

Neutropaenia and thrombocytopaenia were the most common laboratory abnormalities observed in GCA patients treated with TCZ. The percentage of patients who experienced an NCI CTC Grade 2 low neutrophil count was 17%, 12%, 2% and 2% in the TCZ QW, TCZ Q2W, placebo + 26 week and placebo + 52 week groups respectively; the percentage of patients experiencing a Grade 3 neutrophil count was 4% (4 patients) in the TCZ QW group and 4% (2 patients) in the TCZ Q2W group. No patient experienced Grade 4 neutropaenia. Review of the clinical listings showed no association between neutropaenia and serious infections.

Thrombocytopaenia was more common in TCZ groups but all cases were NCI-CTC Grade 1 (7% (7 patients) in the TCZ QW group, 10% (5 patients) in the TCZ Q2W group and 1 patient in the PBO + 52 week group) and none were associated with a bleeding event. The majority of patients across all treatment groups had normal platelet counts for the

duration of the study. Mean and median platelet counts decreased after the first TCZ dose and remained at the lower end of the normal range for the remainder of the 52 week treatment period.

Increased transaminases and elevated bilirubin were observed in a higher percentage of patients in the TCZ QW and TCZ Q2W groups than in either of the placebo groups; however, no patients were identified as having > 3 x the upper level of normal (ULN) elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and 2 x ULN in total bilirubin (Hy's law criteria). Analysis of ALT/AST levels by NCI CTC grade shows that the majority of patients across all treatment groups had normal ALT/AST levels for the duration of the study and among those with elevated ALT/AST, most experienced a Grade 1 value. One patient in each of the TCZ QW and TCZ Q2W groups had a Grade 2 elevated ALT value, while 2 patients in the TCZ QW group and 1 patient in each of the TCZ Q2W and PBO + 52 week groups experienced a Grade 3 elevated ALT value.

After initiation of treatment, the percentage of patients who had a shift from Baseline to a worse total cholesterol value (that is, a shift to a higher ATP III category);[38] was higher in the TCZ QW (38%; 30/79) and TCZ Q2W (40%; 18/45) treatment groups than in the placebo + 26 week (19%; 8/42) and placebo + 52 week (26%; 11/42) groups. The percentage of patients who had a shift from Baseline to a worse low density lipoprotein (LDL) cholesterol value was also higher in the TCZ QW (77%; 77/100) and TCZ Q2W (67%; 32/48) groups than in the placebo + 26 week (42%; 21/50) and placebo + 52 week (48%; 23/48) groups.

The rates of potential hypersensitivity reactions were low and comparable between the TCZ and placebo groups. 3 patients had hypersensitivity reactions reported as SAEs. No clinically significant anaphylactic events were reported.

The proportions of patients in the study who developed anti-drug antibodies (ADA) were overall low (1.1% – 6.5%) across all treatment arms. One patient in the TCZ QW group and 3 patients in the TCZ Q2W group developed treatment induced ADAs after TCZ treatment. Among these 4 patients, none experienced anaphylaxis, clinically significant hypersensitivity or injection site reactions. The overall proportion of patients withdrawn from the study due to a lack of therapeutic response was low (2.0% to 6.1%) across all treatment groups. Among patients in the Safety Population who withdrew due to lack of therapeutic response, none developed a treatment induced ADA.

The rates of malignancies were numerically lower in the TCZ groups compared to the placebo groups. The follow up period (52 weeks) was short with respect to assessment of malignancies.

The safety of QW versus Q2W was not significantly different except for a slightly higher incidence of neutropaenia and infection with QW dosing. The proposed PI has dosage modification recommendations to manage the risk of neutropaenia.

Overall, the safety profile observed with SC TCZ in Study WA28119 (Part 1) was generally consistent with the established safety profile of IV TCZ in RA (except for injection site reactions, known to be associated with SC administration and not IV). No new signals were observed in the pivotal Study WA28119.

The PI advises that treatment should be initiated by healthcare professionals experienced not only in the diagnosis and treatment of GCA but also in the use of biological therapies. The PI provides guidance on monitoring of laboratory parameters and dose modifications to manage abnormal results.

[38] The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III)

The sponsor submitted a real world data study to characterise the longer term risk associated with the use of glucocorticoids in GCA. This study provided evidence of a significant increase in the risk of a glucocorticoid related AE with each 1 g increase in cumulative glucocorticoid dose. The study also reported that patients in real world clinical practice were exposed to higher cumulative glucocorticoid doses than those in the Study WA28119 control groups. These findings are relevant in light of the glucocorticoid sparing effect of TCZ demonstrated in Study WA28119.

Risk management plan

The clinical evaluator has advised that the Summary of Safety Concerns in this Risk Management Plan is satisfactory.

The RMP evaluator has advised that patient questionnaire forms in Annex 7 of the EU-RMP need to be modified to collect Australian Indigenous identity status.

The RMP evaluator has flagged a concern that the sponsor does not intend to include the CMI in the product packaging. The proposed CMI contains detailed instructions, including clear graphics, to guide patients with self-injection. This consumer friendly information is not available in the PI, which is included in the packaging of injectable products as a standard condition of registration. The sponsor has advised that the PI, but not the CMI, will be included in the packaging for Actemra, noting that the CMI can be obtained by other means. The RMP evaluator has asked the sponsor whether the 'Actemra for me' patient guide, which contains instructions for administration, is still actively distributed. The evaluator has also requested the sponsor to provide recent distribution metrics demonstrating that patients initiated on Actemra for self-injection receive this information. If this guide is not being provided to patients initiated on Actemra, then the RMP evaluator considers that the sponsor should provide the CMI in the packaging, in addition to the PI, so that patients have an immediately available reference to support correct self-injection technique.

The RMP evaluator recommends the following condition of registration:

- Implement EU-RMP (version 21.0, date 11 November 2016, data lock point October 2016) with Australian Specific Annex (version 6.0, date November 2016) and any future updates.

Risk-benefit analysis

Delegate's considerations

Efficacy

The pivotal study was well designed with use of a clinically meaningful efficacy endpoint of sustained remission at Week 52 (off prednisone for 6 months). The use of 2 double blind, variable dose, and variable duration prednisone tapering regimens as the comparator is representative of current clinical practice. This study is representative of the intended patient population in Australia, so the findings of this study are applicable to the Australian context.

The pivotal Study WA28119 met its primary and key secondary endpoints, demonstrating superiority over placebo + 26 or 52 week prednisone taper for both the QW and Q2W TCZ regimens. Efficacy of TCZ was demonstrated across different subgroup analyses. Both TCZ regimens were associated with fewer disease flares compared with placebo. Average cumulative prednisone doses were significantly lower in the TCZ groups compared to the

placebo groups. This reduction in corticosteroid exposure is considered to be clinically meaningful with respect to decreasing the toxicity burden of prolonged corticosteroid use.

Safety

The overall safety profile observed in the Actemra treatment groups in Study WA28119 was generally consistent with the known safety profile. No new safety signals were observed. Evidence for safety of treatment of GCA beyond 52 weeks was not provided in this submission, though this product does have a longer history of use for the RA indication and postmarket safety monitoring has not revealed new or unexpected concerns with the SC formulation.

Indication

The clinical evaluator has recommended that the indication be changed from treatment of GCA to treatment of active GCA, on the basis that all patients enrolled in the pivotal study were required to have had active disease within 6 weeks of the baseline randomisation visit. The sponsor does not accept this recommendation because it may suggest to treating physicians that Actemra should be stopped once the disease has been brought under control rather than continuing treatment at the physician's discretion to maintain disease control. In USA and Europe, TCZ is approved for treatment of adult patients with GCA.

The Delegate agrees that treatment with Actemra should be initiated on the basis of the patient having active disease but has some concern that specifying 'active' in the indication may create uncertainty regarding continuing treatment in patients whose disease has responded to treatment and is in remission. In the pivotal study, patients continued with Actemra treatment beyond induction of remission. Advice from ACM is sought on this issue, but at this stage, the Delegate's preference is for the current proposed indication.

Dose frequency

The proposed dosage of 162 mg once every week by SC injection (the same dosage as for RA) is supported by the clinical evaluator. The PI contains dose modification recommendations for managing liver enzyme abnormalities, low neutrophil count and low platelet count.

The US PI recommends 162 mg once every week by SC injection for GCA but also includes a statement that a dose of 162 mg once every other week may be prescribed based on clinical considerations. There are similar dose modification recommendations for managing laboratory abnormalities. EU dosage recommendations for GCA are not yet published.

The pivotal study demonstrated superiority of both QW and Q2W dosing over placebo. With regard to the relative efficacy of QW and Q2W regimens, there was a small difference in the primary endpoint of sustained remission at Week 52 in favour of the proposed QW dosing. Consistent trends favouring QW over Q2W TCZ were seen for other endpoints and subgroup analyses. TCZ exposure was approximately 5.5 fold higher following QW administration compared to Q2W. There was a higher incidence of neutropaenia with QW dosing but this risk can be managed with dose modifications. There was also a higher incidence of infections in the QW group compared to Q2W, but this was still lower than the placebo + 52 week taper group. The safety profiles of both QW and Q2W dosing are considered acceptable.

The efficacy and safety of the QW and Q2W regimens for the treatment of GCA have been satisfactorily established. The demonstrated advantages of QW over Q2W dosing are small and data regarding relapse rates in the extension study for the 2 dosage regimens are not yet available for evaluation. Advice from ACM is sought regarding the proposed dosage. At this stage, the Delegate's view is that 162 mg once every week is acceptable as the recommended dosage but it would be appropriate to include a statement in the PI that 162 mg every other week may be prescribed based on clinical considerations.

Treatment duration

There is limited efficacy data beyond 52 weeks. In the pivotal study, patients in remission at Week 52 ceased treatment with TCZ and are being followed up in the open label extension phase (Part 2). The objective is to assess the long term safety and maintenance of efficacy after 52 weeks of therapy with TCZ, to explore the rate of relapse and the requirement for TCZ therapy beyond 52 weeks and to gain insight into the potential long term steroid sparing effect of TCZ. The Clinical Study Report for Part 2 of Study WA28119 is expected in the first quarter of 2019.

The clinical evaluator's recommendation that treatment beyond 52 weeks should be guided by disease activity, physician assessments, patient choice and emerging data including but not limited to, the long term data from Study WA28119 is reasonable.

Home based use

Home based use of SC TCZ was approved in Australia for the RA indications in 2016 and is also approved in USA, EU, Canada and New Zealand. No new concern has been identified in relation to home based use for GCA. Guidance in the PI regarding home based treatment for GCA is the same as the guidance provided for the RA indications.

RMP

The RMP evaluator recommends that the CMI, or appropriate instructions for use, be included in the packaging to promote safe use of Actemra in home treatment.

The RMP evaluator advises that the patient questionnaire forms in Annex 7 of the EU-RMP should be modified to collect Australian Indigenous identity status.

Data deficiencies

Evidence for efficacy and safety of TCZ treatment for GCA beyond 1 year is limited. The optimal duration of treatment remains uncertain and may be informed by the results of the long term extension study.

Conclusion

The clinical evaluator has recommended approval of this application for a new indication subject to PI changes specified in the evaluation report and a commitment to submit the data from the long term extension phase of Study WA28119. The RMP evaluator has proposed a modification to questionnaire forms and has also flagged a concern that the sponsor does not intend to include the CMI, which contains patient oriented instructions for use, in the packaging. Advice is sought from the TGA's Advisory Committee on Medicines (ACM) regarding the proposed indication and dosage recommendation. At this stage, subject to the advice of ACM, amendments to the PI and resolution of the issues raised by the RMP evaluator, the Delegate considers that this application for a new indication could be approved.

Proposed conditions of registration

The following are proposed as conditions of registration:

1. Implement EU-RMP (version 21.0, date 11 November 2016, data lock point October 2016) with Australian Specific Annex (version 6.0, date November 2016) and any future updates.
2. Submit the final study report from the open label extension phase of Study WA28119 as a category 1 submission.

Summary of issues arising from this submission

Indication

The evaluator has recommended that the indication should refer to treatment of active GCA on the basis that all patients enrolled in the pivotal study were required to have active disease within 6 weeks of the baseline randomisation visit. The sponsor does not agree with this recommendation because of concern that it will suggest to treating physicians that treatment with Actemra should be stopped once the disease has been brought under control, rather than continued at the physician's discretion to maintain disease control. Neither the USA nor European indications specify 'active' GCA.

Dosing frequency

The pivotal study found that both weekly and every other week (Q2W) dosing were superior to placebo, with small numerical differences in favour of weekly dosing over Q2W for the primary endpoint and other endpoints and secondary analyses. Weekly dosing achieved mean exposure 5.5 times higher than Q2W dosing. Safety was broadly similar for weekly and Q2W dosing, other than small increases in neutropaenia (which can be managed with adjustments to dosing) and infections.

Consumer information

Further information is sought from the sponsor regarding the availability of appropriate consumer friendly information to support safe use of this product in the home setting. The sponsor has indicated that it does not intend to include the CMI in the product packaging. The RMP evaluator recommends that appropriate instructions for use should be readily available to patients initiated on Actemra.

Proposed action

The Delegate had no reason to say, at this time, that the application to register a new indication for Actemra should not be approved.

Request for ACPM advice

1. Does the committee agree with the recommended dose of 162 mg once weekly? Does the committee consider that the PI should contain additional guidance that 162 mg every other week may be prescribed based on clinical considerations?
2. The committee was 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

Sponsor's comment on the Delegate's proposed action and advice sought

In this response, the sponsor makes comment on the issues for which the Delegate has sought Advisory Committee on Medicines (ACM) advice. Responses to the Delegate's questions for the sponsor are also provided.

Indication

The sponsor considers the originally proposed indication as appropriate:

> *'Actemra is indicated for the treatment of giant cell arteritis (GCA) in adult patients.'*

All patients enrolled in pivotal Study WA28119 were required to have active disease within 6 weeks of the baseline randomisation visit. The indication as originally proposed is considered appropriate as it is intended that GCA patients should continue with Actemra treatment (at the physician's discretion) beyond induction of remission in order

to maintain disease control and therefore specifying 'active' is not required. Inclusion of the word 'active' in the indication may create uncertainty regarding continuing treatment in patients whose disease has responded to treatment and is in remission.

The proposed indication in Australia is consistent with that approved in the USA and EU (CHMP positive opinion).

Dosage

The sponsor considers the weekly (QW) dosage schedule as the appropriate starting dose for all patients.

The proposed QW dosage schedule is the appropriate starting dose for all patients, with the every other week (Q2W) dosage reserved for dose modification in the event of certain laboratory abnormalities.

The sponsor recommends QW dosing for the treatment of GCA based upon consistent evidence of incremental efficacy with the QW regimen together with a lack of safety issues that would preclude this recommendation. The results of pivotal Study WA28119 showed that both QW and Q2W dosing were superior to placebo but small numerical differences were consistently observed in favour of QW dosing for the primary and other efficacy endpoints regardless of patient subgroup. The safety of QW dosing was broadly similar to that of Q2W dosing; the only notable exceptions were higher incidences of neutropaenia, which can be managed with dose modification, and infections which were still lower than with placebo.

Sustained remission

While the primary and key secondary endpoints were met by patients in both the Actemra treated groups, a slightly higher percentage of responders were observed in the QW group.

A post hoc analysis of the time to GCA flare also revealed a numerically better response to treatment for the QW regimen over the Q2W regimen.

When time to first GCA disease flare is expressed as relapse free survival using Kaplan-Meier plots over the course of the 52 week blinded phase of the study in the intent to treat (ITT) population, there is a distinct separation between the survival profiles of the 2 Actemra treatment groups. The initially overlapping survival curves for the QW and Q2W groups start to separate between Weeks 20 and 24, a critical time point in the study when patients started to discontinue prednisone in accordance with the protocol defined taper; this is consistent with the concept that the more frequent Actemra administration is essential to the maintenance of disease remission upon discontinuation of glucocorticoids.

Patients with potentially more refractory/severe disease

With respect to relapse free survival over 52 weeks, the separation between the Q2W group and the QW group observed in the ITT population is far more pronounced in the relapsing patient subgroup and suggestive of an even greater resistance to flare upon tapering and discontinuation of glucocorticoids in the QW group compared to the Q2W group.

Relapsing patients present an additional dimension to the challenges facing treating physicians during the course of managing GCA. This group of patients represents those who have already been exposed to high dose and long duration glucocorticoid regimens. When these patients relapse, physicians have little choice but to re-start or to increase the dose of glucocorticoid therapy as there are currently no proven glucocorticoid sparing therapies.

New onset patients represent a different challenge in that new GCA patients are at highest risk for vision loss and therefore require immediate aggressive immunomodulation.

Although there was broad overlap in the survival curves between the 2 Actemra groups in the new onset patients, the consequences of flares in these patients can be devastating. In addition, these patients will suffer from exposure to high dose glucocorticoids if their disease is poorly controlled from the start. It is therefore crucial that patients presenting with newly diagnosed GCA are treated with the most effective available dose of Actemra. A quality of life study focusing on GCA demonstrated that, in addition to their fear of vision loss, the factor that affected patients' quality of life most adversely was the need for recurrent, chronic courses of glucocorticoids.[39]

Cumulative glucocorticoid dose

Patients who flared in the Q2W group received over 700 mg more cumulative prednisone (based on medians) than those who flared in the QW group suggesting that patients in the Q2W group were more difficult to treat when they flared compared to patients who flared in the QW group. This is of clinical importance with respect to the prognosis relating to subsequent glucocorticoid related toxicity.

The QW group demonstrated a meaningful decrease compared to both placebo groups in cumulative glucocorticoid dose at Week 52 in both new onset and relapsing patients. This was also observed for the Q2W group in relapsing patients, while new onset patients treated with Q2W showed a less pronounced reduction in cumulative glucocorticoid doses from those seen in the placebo + 26 week group.

Comparable safety

The safety profile of Actemra in combination with a 26 week glucocorticoid tapering regimen was comparable to that observed in patients treated with either 26 weeks or 52 weeks of glucocorticoids alone. Very similar proportions of patients in the QW and Q2W groups experienced any AE or serious AE. Taken together with the totality of the safety data described in the Summary of Clinical Safety (including a comparison with the safety profile of Actemra in the treatment of rheumatoid arthritis), the sponsor considers there to be no safety reason to preclude recommending the QW dose for the treatment of GCA.

Longer term disease control

Patients in remission at Week 52 stopped their Actemra injections and are being followed up off Actemra during the open label extension phase (Part 2) of the study.

Preliminary data from 45 patients that met the primary endpoint in Part 1 and were followed for at least an additional 48 weeks revealed that a higher proportion of patients that previously received Q2W experienced a GCA flare (73%, 8/11) in Part 2 compared to those who previously received QW (33%, 8/24). This is consistent with the concept that the QW regimen may be more effective at suppressing disease activity than the Q2W dose.

Expert opinion and conclusion

The QW dosing recommendation is supported by an international group of GCA specialists who attended the Actemra GCA Advisory Board Meeting in London from July 28 to 29, 2016. The expert rheumatologists and ophthalmologists unanimously confirmed the clinical opinion that the QW regimen was the appropriate choice for treating patients with GCA. GCA represents a medical emergency, requiring immediate and adequate initiation of treatment to prevent sudden vision loss and other ischaemic complications in patients with GCA. None of the expert panel wanted to put patients or their physicians in the position of wondering if an adverse vision or other vascular outcome might have been prevented by use of the QW as opposed to the Q2W Actemra dosing regimen.

[39] Hellmann DB, Uhlfelder ML, Stone JH, et al. Domains of health-related quality of life important to patients with giant cell arteritis. Arthritis Rheum. 2003;49(6):819-25

The Q2W dosage is, however, considered to be an important dose modification tool for the management of certain laboratory abnormalities (elevated liver enzymes, low absolute neutrophil count, and low platelet count) as described in the proposed PI.

Sponsor's responses to the Delegate's questions

1. *How does the sponsor propose to address the concern about patients having reliable access to consumer friendly information to support safe treatment in the home?*

Sponsor's response

The instructions for Health care professionals (HCPs) in the PI and the patient friendly information in the CMI are appropriate to support safe administration of Actemra in the home for GCA patients. The PI will be provided in the pack and both HCPs and patients will be able to access the CMI through a variety of different mechanisms.

The PI instructs HCPs to provide appropriate patient training on the injection technique, to make an assessment for suitability of patients for home use and ensure follow up as necessary. The PI states at least the first injection must be performed under the supervision of a qualified HCP. After proper training in injection technique, patients may self-inject with Actemra only if their treating physician determines that it is appropriate and is satisfied that the patient can safely self-inject in the home environment and with medical follow up as necessary.

Detailed instructions to support safe treatment in the home are also provided in the CMI. The CMI will be distributed through the Guildlink Secure Data Warehouse which ensures the CMI is published to the TGA website and the Roche Australia corporate website. It will also be available on the TGA's new MedSearch app. Many different organisations access the CMI through the Guildlink Secure Data Warehouse including Monthly Index of Medical Specialities (MIMS), pharmacy organisations (such as National Pharmacies, Terry White, Chemmart), the Royal Australian College of General Practitioners and Australian Medicines Handbook and these organisations in turn publish the CMI via their publications. In addition, Guildlink distributes the CMI to software vendors to be included in both prescribing and hospital and community pharmacy dispensing software programmes, thus ensuring the availability of the CMI to the patient at the time of prescribing or the point of dispensing.

Delegate's question

> *'With reference to the Clinical Evaluation Report, the plot of cumulative prednisone dose to Week 52 does not appear to match the accompanying summary table. The table indicates that the median cumulative prednisone dose at Week 52 for the TCZ Q2W regimen was 1862 mg (same as TCZ QW) and for PBO + 26 week taper was 3296 mg, yet these figures do not appear to be accurately reflected in the plot'.*

Sponsor's response

The referenced table summarises the cumulative prednisone dose for all patients, including those who withdrew from the study early. The referenced figure is based on observed data at each visit and therefore summarises the patients who are still in the study at each visit; hence the Week 52 results are based only on the subset of patients who completed the study and had available data at Week 52.

Advisory Committee Considerations

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

The ACM taking into account the submitted evidence of efficacy and safety, agreed with the Delegate and considered Actemra 162 mg/0.9 mL solution for injection pre-filled syringe; injection concentrated vial containing 162 mg/0.9 mL; 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL of tocilizumab to have an overall positive benefit-risk profile for the addition of the proposed indication:

Giant Cell Arteritis (SC formulation only)

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

In making this recommendation the ACM:

- Noted the evidence regarding the use of TCZ in the treatment of giant cell arteritis.
- Was of was of the view that the sponsor should provide the consumer medicines information leaflet in the package.
- Noted that the sponsor currently provides a patient support program for Actemra.

Specific Advice

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

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

1. Does the committee agree with the current proposed indication?

The ACM considered that the pivotal Phase III Study WA28119, and the supporting Phase II Study ML25676 provided by the sponsor demonstrated a reduction in relapse rate and a prednisolone sparing effect in new onset and relapsed giant cell arteritis (GCA). The committee accepted that the efficacy and safety of tocilizumab for the treatment of GCA in adult patients has been established. The committee noted that data on use beyond 52 weeks was limited and discussed concerns regarding duration of TCZ treatment. It was suggested that the PI communicates that data on use beyond 52 weeks is limited.

The committee discussed the clinical evaluator's recommendation to include 'active' in the indication, but considered that this would not adequately define different clinical scenarios. The committee concluded that the proposed indication is preferable.

2. Does the committee agree with the recommended dose of 162 mg once weekly? Does the committee consider that the PI should contain additional guidance that 162 mg every other week may be prescribed based on clinical considerations?

The ACM considered that both doses of 162 mg once a week and 162 mg once every two weeks were appropriate. The pivotal Phase III study (WA8119) demonstrated that there was no statistically significant difference between these two doses. The committee noted that the toxicity of TCZ is well described in other indications and that giant cell arteritis is commonly seen in elderly patients who are more susceptible to toxicity. Lower doses may mitigate this toxicity and the committee considered that the Dosage and Administration section of the PI should reflect that both doses are acceptable and that weekly dosing should not be preferred over every other week.

3. The committee was 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.

The committee recommended that the sponsor provides a copy of the consumer medicines information leaflet in the package to assist patients in the administration of treatment.

The ACM 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 (TCZ 162 mg/0.9 mL solution) for SC injection, indicated for:

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

Specific conditions of registration applying to these goods

1. The TCZ EU-Risk Management Plan (EU-RMP), version 21.0, date 11 November 2016, data lock point October 2016) with Australian Specific Annex (version 6.0, date November 2016), updated to include the commitment to revise and distribute the patient and healthcare professional brochures for the giant cell arteritis indication, and any future updates., included with submission PM-2016-03548-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The 'Actemra for me' patient brochure is to be updated (inclusive of the current and new indication), or an equivalent brochure only for the new indication is developed, and provided to the TGA prior to marketing.
3. The HCP administration guide is to be updated as required to refer to the new indication, and provided to the TGA prior to marketing.
4. The ASA v6.0 is to be updated to include the new educational material for GCA in Annex 3 and any additional risk minimisation activity for GCA, in addition to the existing 'Additional RMinA for RA: Subcutaneous' of providing HCP brochure and patient brochure
5. The following final study report must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission:
   - the open-label extension phase of WA28119

Attachment 1. Product Information

The PI for Actemra approved with the submission which is described in this AusPAR 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

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au