



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Tocilizumab (rch)

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

August 2020

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- 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.

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Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine aminotransferase
ASA	Australian specific Annex
AUC	Area under the concentration time curve
AUC _{2weeks,ss}	Area under the concentration time curve at steady state at 2 weeks
BMI	Body mass index (kg/m ²)
BSA	Body surface area (m ²)
BW	Body weight
CAR	Chimeric antigen receptor
CHAQ-DI	Childhood Health Assessment Questionnaire-Disability Index
CI	Confidence interval
C _{max}	Maximum plasma concentration
C _{max,ss}	Maximum plasma concentration at steady state
C _{min}	Minimum plasma concentration
C _{min,ss}	Minimum plasma concentration at steady state
CORE	Core part of the clinical study
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical study report
DLP	Data lock point
DMARD(s)	Disease-modifying anti-rheumatic drug(s)
EMA	European Medicines Agency (European Union)
ESR	Erythrocyte sedimentation rate

Abbreviation	Meaning
EU	European Union
EU-RMP	European Union-risk management plan
FDA	Food and Drug Administration (United States of America)
GCA	Giant cell arteritis
GVP	Good Pharmacovigilance Practice(s)
HCP	Healthcare professional
IgG1	Immunoglobulin G1
IL	Interleukin
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
ISR	Injection site reaction
IV	Intravenous/intravenously
JADAS-71	Juvenile Arthritis Disease Activity Score (71 joints)
JIA	Juvenile idiopathic arthritis
LTE	Long term extension
mIL-6R	Membrane bound interleukin 6 receptor
MTX	Methotrexate
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
OLE	Open label extension
PD	Pharmacodynamic(s)
PI	Product Information
<u>pJIA</u>	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic(s)/pharmacodynamics(s)
popPK	Population pharmacokinetic(s)

Abbreviation	Meaning
PSUR(s)	Periodic safety update report(s)
PY	Patient (or person) years
Q10D	Once every 10 days
Q2W	Once every 2 weeks
QW	Once weekly
RA	Rheumatoid arthritis
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous/subcutaneously
SD	Standard deviation
SDS	Standard deviation score
sIL-6R	Soluble interleukin-6 receptor
sJIA	Systemic juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics (European Union)
TCZ	Tocilizumab
URTI	Upper respiratory tract infection
VAS	Visual Analogue Scale

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of Indications
<i>Active ingredient:</i>	Tocilizumab (rch)
<i>Product name:</i>	Actemra
<i>Decision:</i>	Approved
<i>Date of decision:</i>	18 March 2020
<i>Date of entry onto ARTG:</i>	24 March 2020
<i>ARTG numbers:</i>	149402, 149403, 149404, 234034, 296808
▼ <i>Black Triangle Scheme</i>	No
<i>Sponsor's name and address:</i>	Roche Products Pty Limited Level 8, 30-34 Hickson Road Sydney NSW 2000
<i>Dose forms:</i>	Injection, concentrated solution Injection, solution
<i>Strengths:</i>	400 mg/20 mL 80 mg/4 mL 200 mg/10 mL 162 mg/0.9 mL
<i>Containers:</i>	Vial Pre-filled syringe Pre-filled pen
<i>Pack sizes:</i>	4 vials, 1 vial 4 syringes, 1 syringe 4 pens, 1 pen
<i>Approved therapeutic use:</i>	<i>Subcutaneous formulation</i> <i>Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 1 year of age and older.</i> <i>Actemra IV and SC can be given alone or in combination with methotrexate (MTX)</i>

Route of administration: Subcutaneous

Dosage: *Subcutaneous dosing regimen*

The recommended dose of subcutaneous (SC) Actemra for patients with systemic juvenile idiopathic arthritis (sJIA) is:

- 162 mg once every two weeks for patients below 30 kg,
- 162 mg once every week for patients \geq 30 kg

Further dosage information is available in the Product Information.

Product background

This AusPAR describes the application by Roche Products Pty Limited (the sponsor) to extend the indications for Actemra (tocilizumab rch), 400 mg/20 mL, 80 mg/4 mL, 200 mg/10 mL concentrated solution for injection vial and 162 mg/0.9 mL solution for injection pre-filled pen and pre-filled syringe, to include dosing via the subcutaneous (SC) route of administration; and to lower the age limit for systemic juvenile idiopathic arthritis (sJIA) treatment from patients aged 2 years old to patients aged 1 year old (SC formulation only). The full indications for sJIA would therefore read:

Systematic juvenile idiopathic arthritis (IV and SC formulations)

Intravenous formulation

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

Subcutaneous formulation

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

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

Tocilizumab is a recombinant humanised monoclonal antibody of immunoglobulin G1 (IgG1). Tocilizumab binds specifically to the cytokine interleukin-6 (IL-6) via the interleukin-6 receptor (IL-6R); binding to both soluble interleukin-6 receptors (sIL-6R) and membrane-bound interleukin-6 receptors (mIL-6R) and has been shown to inhibit both sIL-6R and mIL-6R mediated signalling. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including arthritis. In clinical studies with tocilizumab, rapid decreases in C-reactive protein (CRP);¹ erythrocyte sedimentation rate (ESR);² and serum amyloid A;³ were observed.

¹ C-reactive protein (CRP) is an acute-phase protein synthesised and secreted by hepatocytes (liver cells) in. Elevation of CRP is a sensitive and accurate marker indicative of inflammation that may be acute or chronic in cause and due to various aetiologies including infection, autoimmune disease and tissue necrosis. Reduction in CRP may in turn be used as a marker of the response to therapy or elimination of the underlying cause of inflammation.

² The erythrocyte sedimentation rate (ESR) is the rate at which erythrocytes (red blood cells) in anticoagulated whole blood descend in a standardised tube over a period of one hour. It is a common hematology test, and is a non-specific measure of inflammation.

³ Serum amyloid A (SAA) proteins are a family of apolipoproteins (lipid-binding proteins) associated with high density lipoprotein (HDL) in plasma. Different isoforms are expressed either constitutively or in response to inflammation by in response to inflammatory stimuli (acute phase SAAs).

Condition being treated

sJIA is a subset of juvenile idiopathic arthritis (JIA) and accounts for 10 to 20% of all JIA cases. The most common manifestations of sJIA at disease onset are fever, arthritis, rash and lymphadenopathy. Other associated manifestations of sJIA include hepatosplenomegaly, splenomegaly, pericarditis and other forms of serositis and pulmonary manifestations such as pleural effusion, interstitial lung disease, alveolar proteinosis and pulmonary hypertension. Macrophage activation syndrome is a severe, life-threatening complication of sJIA. Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, methotrexate and biologic agents that inhibit interleukin-1 (IL-1) or IL-6.

Regulatory status

Tocilizumab is available in intravenous (IV) and SC forms. Tocilizumab for IV infusion was first entered onto the Australian Register of Therapeutic Goods (ARTG) in Australia in 2009 for the rheumatoid arthritis (RA) indication. 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 sJIA in patients aged ≥ 2 years and in October 2013 for patients with polyarticular JIA (pJIA) in patients aged ≥ 2 years. 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. In 2017, the indications were further extended to include giant cell arteritis (GCA), for SC use only. In November 2018, a new route of administration (SC) was approved for patients aged ≥ 2 years with pJIA.

In March 2019, the indications were further extended to include the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older, for IV use only.

The full indications at the time the submission was under consideration were:

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 in combination with MTX in those not previously treated with MTX;

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

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

Giant cell arteritis (SC formulation only)

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

Polyarticular juvenile idiopathic arthritis (IV and SC formulations)

Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an

inadequate response to or intolerance to methotrexate (MTX). Actemra can be given alone or in combination with MTX.

Systematic 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).

Cytokine release syndrome (CRS) (IV formulation only)

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

At the time the TGA considered this application, similar applications had been approved in the European Union (EU), United States (US), and Canada. The extension of indication for SC tocilizumab (pre-filled syringe) to include the treatment of active sJIA in patients 1 year of age and older, weighing at least 10 kg was approved in the EU on 29 October 2018. The Food and Drug Administration (FDA) approved SC tocilizumab for use in sJIA patients on 13 September 2018 but did not lower the age limit from 2 years to 1 year of age. On 21 March 2019, Health Canada approved the following indication for both the IV and SC formulations of tocilizumab:

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with one or more non-steroidal anti-inflammatory drugs and systemic corticosteroids.

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 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-05341-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	22 February 2019
First round evaluation completed	1 July 2019
Sponsor provides responses on questions raised in first round evaluation	30 July 2019
Second round evaluation completed	13 September 2019

Description	Date
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	19 December 2019
Sponsor's pre-Advisory Committee response	21 January 2019
Advisory Committee meeting	7 February 2020
Registration decision (Outcome)	18 March 2020
Completion of administrative activities and registration on ARTG	24 March 2020
Number of working days from submission dossier acceptance to registration decision*	242

*Statutory timeframe for standard applications is 255 working days

III. Submission overview 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 dossier contained the following clinical study reports (CSRs) relevant to this application:

- Population pharmacokinetic (popPK) and pharmacokinetic-pharmacodynamic (PK/PD) analyses report - popPK analysis of tocilizumab of Studies WA19977 and WA28117 and graphical exposure-efficacy and -safety analyses of Study WA28117 in patients with polyarticular juvenile idiopathic arthritis, final version 14 June 2017. Report 1074871;
- PopPK and PK/PD report - population pharmacokinetic analysis and exposure-efficacy and safety analyses of tocilizumab for Study WA19977 in paediatric patients with polyarticular juvenile idiopathic arthritis. Report 1049415;
- PopPK and PK/PD analyses report - popPK analysis of tocilizumab SC and IV (Studies WA28118 and WA18221) and graphical exposure-safety and exposure-efficacy

analysis of tocilizumab SC (Study WA28118) in patients with systemic juvenile idiopathic arthritis final version 27 February 2018. Report 1084039;

- CSR – Study WA28118 – sJIA;
- CSR – Study WA28117 – pJIA;
- CSR – Study NA25220 (core part (CORE)): tocilizumab SC versus placebo SC rheumatoid arthritis. Primary analysis at Week 24;
- CSR – Study NA25220 (long term extension (LTE)) tocilizumab SC versus placebo rheumatoid arthritis. Final results of the open-label extension (OLE);
- CSR - Study WA22762 (CORE): tocilizumab SC versus tocilizumab IV, in active rheumatoid arthritis;
- Final CSR - Study WA22762: tocilizumab IV rheumatoid arthritis;
- CSR – Study WA18221 sJIA;
- Nine literature references.

Pharmacology

Pharmacokinetics

Study WA28118

Study WA28118 was a Phase Ib, 52 week, open-label, multicentre study to investigate the pharmacokinetics (PK), pharmacodynamics (PD) and safety of tocilizumab following SC administration to sJIA patients. The study aimed to determine the appropriate SC dosing regimen across the range of body weights (BW) in patients with sJIA aged 1 to 17 years in comparison to the exposure obtained in Study WA18221, which demonstrated the efficacy and safety of IV tocilizumab in patients with sJIA. Patients with sJIA and a history of inadequate response to NSAIDs and corticosteroids were included in the study. Patients were excluded if they had previously discontinued IV tocilizumab therapy due to inadequate response or safety events, had poorly controlled disease despite IV tocilizumab therapy or if their disease was well controlled by other treatments. Patients were either naïve to tocilizumab therapy or switched from tocilizumab IV to tocilizumab SC at Baseline.

Dosing was based on body weight:

- Patients weighing < 30 kg enrolled prior to interim analysis: tocilizumab SC once every 10 days (Q10D);
- Patients weighing < 30 kg enrolled after interim analysis: tocilizumab SC once every 2 weeks (Q2W);
- Patients weighing \geq 30 kg: tocilizumab SC once weekly (QW).

The dosing interval of tocilizumab could be adjusted according to changes in BW after Week 14. The first four SC injections were administered under supervision of the investigator in a setting where medications and resuscitation facilities were available.

An interim analysis of the first 28 patients who completed Week 14 showed a higher than anticipated steady-state minimum plasma concentration ($C_{\min,ss}$) following the Q10D dosing regimen, especially for lighter patients, due to a higher bioavailability of tocilizumab SC observed in sJIA patients (93.9%) compared with adult RA patients (79.0%). The dosing regimen for patients < 30 kg was changed to Q2W.

A total of 57 patients were screened and 51 were enrolled (25 in the < 30 kg group and 26 in the \geq 30 kg group). Prior tocilizumab treatment was reported for 40% of the < 30 kg

patients and 57.7% of the ≥ 30 kg patients. Seven patients withdrew (13.7%), 4 out of 7 because of decreased efficacy, 2 deaths (both in < 30 kg patient group), and one due to persistently low neutrophil counts.

The majority of the patients were female (56.9%), white (80.4%) and of non-Hispanic or Latino ethnicity (76.5%). The < 30 kg BW group were younger (median age 5 years versus 14 years), shorter (median height 104.5 cm versus 154.8 cm), and lighter (median weight 19.6 kg versus 51.7 kg), than the ≥ 30 kg BW dosing group. Three patients were under the age of 2 years at Baseline.

At Baseline, background oral corticosteroids were taken by 80% of the < 30 kg group and 46.2% of the ≥ 30 kg group. Previous use of non-biologic disease-modifying anti-rheumatic drugs (DMARDs) was 56% and 92.3%; biologic DMARD was 56.0% and 88.5%, and background methotrexate use was 52.0% and 53.8% of the < 30 kg and ≥ 30 kg groups, respectively.

A total of 832 PK samples were collected from 51 patients. The observed median minimum plasma concentration (C_{min}) for tocilizumab naïve and prior tocilizumab patients by dosing regimen is described below in Table 2. A higher C_{min} was observed for the < 30 kg BW Q10D dosing regimen compared to both the < 30 kg BW Q2W and the ≥ 30 kg BW QW dosing regimens. The results of model-computer PK parameters are discussed under 'Population pharmacokinetic data', below.

Table 2: Study WA28118 Minimum tocilizumab serum concentrations by visit, by tocilizumab status and body weight

Median C_{min} (range) in $\mu\text{g/mL}$	TCZ naïve (n = 26)			Prior TCZ (n = 25)		
	< 30 kg		≥ 30 kg	< 30 kg		≥ 30 kg
	Q10D (n = 3)	Q2W (n = 12)	QW (n = 11)	Q10D (n = 5)	Q2W (n = 5)	QW (n = 15)
Week 14	n = 3 116.0 (91.8–256.0)	n = 11 41.4 (12.8–114.0)	n = 10 71.5 (28.1–136.0)	n = 4 82.2 (40.7–186.0)	n = 5 93.8 (39.0–102.0)	n = 10 94.7 (33.7–213.0)
Week 38	n = 3 127.0 (120.0–347.0)	n = 10 69.2 (4.6–122.0)	n = 11 65.5 (22.7–136.0)	n = 3 86.2 (52.5–199.0)	n = 5 90.4 (51.7–101.0)	n = 12 92.3 (25.2–152.0)
Week 52	n = 2 247.0 (125.0–369.0)	n = 9 51.7 (14.6–106.0)	n = 10 58.3 (38.3–132.0)	n = 2 92.2 (60.3–124.0)	n = 5 80.6 (65.3–84.2)	n = 10 84.7 (27.1–155.0)

TCZ = tocilizumab

Population pharmacokinetic data

The aim of the popPK analysis was to describe the PK properties of tocilizumab following multiple IV and SC dosing in patients with sJIA, to identify covariates that influence tocilizumab PK in these patients, and to compare tocilizumab exposure following IV (Q2W, 12 mg/kg for BW < 30 kg and 8 mg/kg for BW ≥ 30 kg) and SC (162 mg, Q2W for BW < 30 kg and QW for BW > 30 kg) dosing. The study used data from sJIA Studies WA18221 and WA28118 in addition to the data used in the prior analysis. Study WA18221 was a 2 year Phase III study of IV tocilizumab in patients with sJIA.

The analysis dataset included 878 PK samples from 89 patients in Study WA18221 and 832 PK samples from 51 patients of Study WA28118 (25 patients with BW < 30 kg and 26 patients with BW ≥ 30 kg). There were only 3 patients < 2 years of age at Baseline (aged 17, 19 and 22 months) in Study WA28118.

The tocilizumab serum concentration-time course was described by a two-compartment PK model with first-order absorption (following SC administration) and parallel linear and

Michaelis-Menten elimination. The most significant covariates contributing to the variability in the PK parameters in sJIA patients were body size measures. Tocilizumab PK parameters (clearance, inter-compartmental clearance, central and peripheral volumes, and maximum target-mediated elimination rate) increased with increasing body surface area (BSA), while SC absorption parameters (absolute bioavailability and absorption rate constant) decreased with increasing body mass index (BMI). Serum creatinine (which increased with age and correlated with body size parameters) also influenced maximum target-mediated elimination rate.

Absolute bioavailability was estimated to be 94.8% and the absorption half-life was estimated to be approximately 2 days following SC administration for a typical sJIA patient with BMI of 18 kg/m².

Model computed median and range for $C_{min,ss}$ and the area under the concentration time curve at steady state at 2 weeks ($AUC_{2weeks,ss}$) were similar following the tocilizumab SC 162 mg Q2W (BW < 30 kg) and QW (BW ≥ 30 kg) regimens, while the median steady-state C_{max} ($C_{max,ss}$) was higher for patients in the < 30 kg BW group compared with the ≥ 30 kg BW group (Table 3, below). More than 95% (n = 49) of sJIA patients treated with tocilizumab SC 162 mg Q2W (BW < 30 kg) and QW (BW ≥ 30 kg) had a model-computed $C_{min,ss}$ at least as high as that achieved with tocilizumab IV.

The majority of sJIA patients receiving tocilizumab SC in both BW groups had a similar or higher C_{min} , a lower median but similar range of steady-state AUC, but a much lower median and range of C_{max} than those achieved with tocilizumab IV.

Table 3: Model computed steady-state pharmacokinetic parameters by regimen and body weight group (median [range])

Dosing regimen	BW Group	$C_{min,ss}$ (µg/mL)	$C_{max,ss}$ (µg/mL)	$AUC_{2weeks,ss}$ (µg/mL × day)
TCZ SC				
162 mg SC Q2W (n = 25)	< 30 kg	64.15 [16.61 – 135.9]	126.6 [51.67 – 265.8]	1298 [539 – 2792]
162 mg SC QW (n = 26)	≥ 30 kg	72.37 [19.52 – 157.8]	89.8 [26.37 – 190.2]	1154 [334 – 2370]
TCZ IV				
12 mg/kg IV Q2W (n = 46)	< 30 kg	65.86 [18.99 – 135.5]	274.4 [148.8 – 444.0]	1734 [840 – 2712]
8 mg/kg IV Q2W (n = 43)	≥ 30 kg	70.73 [5.26 – 126.6]	253.0 [119.6 – 404.3]	1631 [526 – 2779]

The number of tocilizumab IV sJIA patients includes all patients randomised to tocilizumab in Part I of Study WA18221, as well as any patient who escaped from placebo to tocilizumab in Part I and had a PK sample available.

The graphical analysis of exposure-safety relationships in sJIA patients from Study WA28118 showed that observed trough concentrations and predicted steady state values were similar in subjects with and without events. Probabilities for adverse events (AE) were not significantly correlated with tocilizumab exposure for all classes of events analysed.

The graphical analysis of the main PD and efficacy parameters in sJIA patients from Study WA28118 showed that similar levels of efficacy (juvenile arthritis disease activity

score complete joint count (JADAS-71)⁴ and childhood health assessment questionnaire-disability index (CHAQ-DI)⁵ were observed across the range of exposures achieved following tocilizumab SC administration, and the variability in tocilizumab exposure was not associated with the variability in efficacy.

Study NP25737

This Phase I study of tocilizumab IV in 11 patients with sJIA aged < 2 years old weighing < 30 kg was evaluated in a previous submission. The study was included due to the limited number of sJIA patients aged < 2 years contributing PK data in Study WA28118. The sponsor supplemented the SC database with model-predicted data from the tocilizumab IV Study NP25737 and performed additional simulations to predict the exposures these patients would have achieved had they received the tocilizumab SC regimen.

In the PopPK model of tocilizumab following IV administration of 8 mg/kg and 12 mg/kg and SC administration of 162 mg, the range of $C_{min,ss}$ achieved with the tocilizumab SC regimens is comparable to that achieved with the approved tocilizumab IV regimens, across the spectrum of BWs seen in the sJIA patient population. However, because tocilizumab SC is administered as a fixed dose (162 mg/0.9 mL SC injection), exposure is inversely correlated with BW, with patients at the lower end of each body weight category experiencing higher tocilizumab concentrations compared to children at the higher end of the BW category. Therefore, for infants aged 1 to 2 years, there is the potential for higher exposure and safety issues with the tocilizumab SC route of administration.

Study WA28118

The simulated $C_{min,ss}$ for the sJIA patients in Study WA28118 are shown in Figure 1. The 3 patients aged < 2 years (shown as red dots) had $C_{min,ss}$ values that were at the higher end for the < 30 kg BW category, but were within the range of $C_{min,ss}$ achieved in patients in the ≥ 30 kg group. Even the highest $C_{min,ss}$ (in the lightest patient aged 25 months with a weight of 9.2 kg) was within the range predicted for patients in the ≥ 30 kg group. Efficacy (via JADAS-71) was maintained or improved in these 4 lightest patients and the safety profile was comparable to that of patients aged ≥ 2 years.

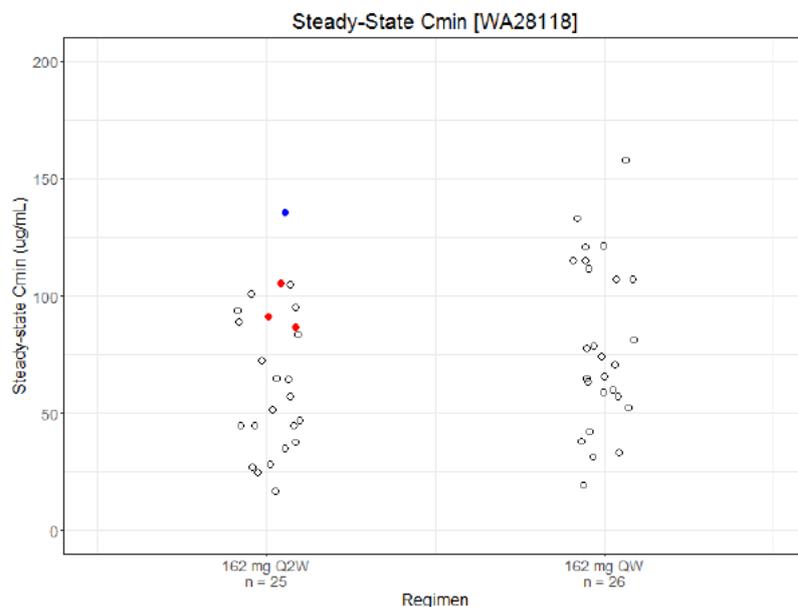
⁴ The **juvenile arthritis disease activity score (JADAS)** is a composite disease activity score for juvenile idiopathic arthritis (JIA) that uses four measures:

- 1) global assessment of disease activity (by physician);
- 2) global assessment of overall wellbeing (by parent/guardian or patient);
- 3) number of joints with active arthritis; and
- 4) erythrocyte sedimentation rate (ESR).

The JADAS-71 uses 71 joints (complete joint count), in addition to the other measures, while the JADAS-27 uses 27 joints, and the JADAS-10 uses 10 joints.

⁵ The **childhood health assessment questionnaire (CHAQ)** is a functional ability assessment questionnaire that covers the child's ability to perform in 8 different functional areas: 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip and 8) activities. Each question is scored from 0 to 3, with 0 being 'no difficulty' and 3 being 'unable to do'. The scores from each of the 8 functional areas are then used to calculate the **childhood health assessment questionnaire-disability index (CHAQ-DI)**, which ranges from 0 to 3, with 0 being the best, and 3 being the worst.

Figure 1: Study WA28118 Simulated steady-state minimum plasma concentration for tocilizumab subcutaneous once every 2 weeks (< 30 kg) or subcutaneous once weekly (≥ 30 kg) in patients with systemic juvenile idiopathic arthritis



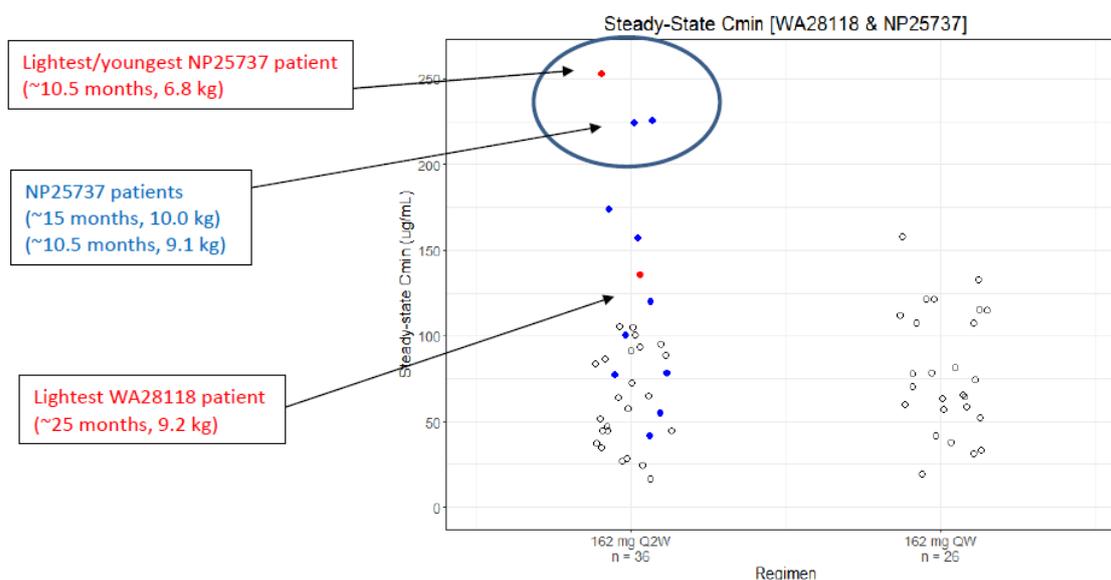
Each circle represents 1 patient. Red dots are patients < 2 years old (n = 3). The blue dot is the lightest patient in Study WA28118 (age 25 months, 9.2 kg).

Study NP25737

Individual PK parameters (post-hoc) obtained for each patient in Study NP25737 were used to simulate the individual tocilizumab concentration-time profiles for these 11 patients aged < 2 years for the 162 mg tocilizumab SC Q2W regimen.

The model-predicted $C_{min,ss}$ values for the tocilizumab SC Q2W regimen for patients aged < 2 years from Study NP25737, and those for patients aged ≥ 1 year in Study WA28118 (tocilizumab SC Q2W and QW) are shown in Figure 2. The majority of patients had $C_{min,ss}$ values within the range seen in Study WA28118 for sJIA patients aged ≥ 1 year. However, 3 patients had higher tocilizumab exposures; one of these patients was aged < 1 year (10.5 months, 6.8 kg), and two patients were aged between 1 to 2 years (15 months, 10.0 kg; 10.5 months, 9.1 kg). The next highest $C_{min,ss}$ values were 174 and 157 $\mu\text{g}/\text{mL}$ in patients aged 15.2 and 13.4 months and weighing 10.4 and 8.9 kg, respectively.

Figure 2: Study NP25737/Study WA28118 Model-predicted steady-state minimum plasma concentration for tocilizumab subcutaneous once every 2 weeks (< 30 kg) or subcutaneous once weekly (\geq 30 kg) in patients with systemic juvenile idiopathic arthritis aged < 2 years (Study NP25737) and \geq 1 year (Study WA28118)



Each circle represents 1 patient. Blue dots are patients from Study NP25737 ($n = 11$). Red dots are the lightest patients from Study NP25737 (< 1 year, 6.8 kg) and Study WA28118 (age 25 months, 9.2 kg).

The steady-state PK parameters (C_{min} , C_{max} , AUC) for tocilizumab SC are compared to the tocilizumab IV regimen in Studies WA18221, WA28118 and NP25737 in Table 4. The maximum steady-state C_{min} and AUC predicted for tocilizumab SC for the sJIA patients in Study NP25737 aged < 2 years (C_{min} 253 $\mu\text{g/mL}$, AUC 3445 $\mu\text{g}\cdot\text{day/mL}$) are higher than seen previously with tocilizumab SC (Study WA28118) or tocilizumab IV (Study WA18221), and are similar to the exposures in Study WA28118 in < 30 kg patients using the SC Q10D regimen (prior to the interim analysis, and dose change to SC Q2W).

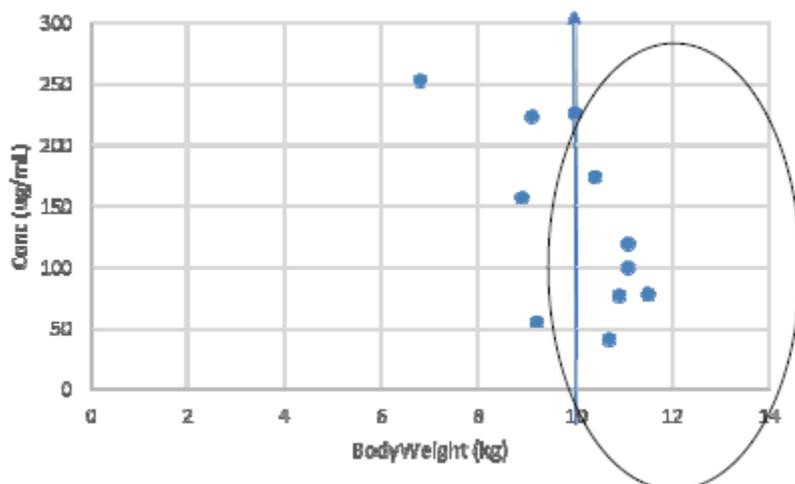
The sponsor then investigated the PK data if a BW cut-off of 10 kg was implemented (Figure 3). This analysis suggested that the steady-state C_{min} would be < 150 $\mu\text{g/mL}$ for the majority of patients, and < 200 $\mu\text{g/mL}$ for all patients, similar to the exposure levels observed in sJIA patients obtained with tocilizumab IV (Study WA18221) and tocilizumab SC (Study WA28118).

Table 4: Summary of model-predicted steady state exposure parameters for systematic juvenile idiopathic arthritis patients receiving tocilizumab subcutaneously (Studies WA28118, NP25737) versus tocilizumab intravenously (Studies WA18221, NP25737)

Dosing regimen	Weight group	n	Median BW (kg) (Min - Max)	C _{min} (µg/mL) Mean ± SD Median (Min - Max)	C _{max} (µg/mL) Mean ± SD Median (Min - Max)	AUC _{0-2weeks} (µg/mL x day) Mean ± SD Median (Min - Max)
Tocilizumab SC in sJIA						
162 mg SC Q2W (Study NP25737)	< 30 kg	11	10.4 (6.8 - 11.5)	137 ± 74.2 119.9 (41.9 - 253.0)	221.3 ± 115.3 195.2 (68.2 - 443.3)	2418 ± 701 2214 (1542 - 3445)
162 mg SC Q2W	< 30 kg	25	19.6 (9.2 - 27.2)	65.86 ± 31.31 64.15 (16.61 - 135.86)	134.1 ± 58.64 126.6 (51.67 - 265.84)	1414 ± 605 1298 (539 - 2792)
162 mg SC QW	≥ 30 kg	26	51.7 (30.0 - 73.2)	79.18 ± 35.57 72.37 (19.52 - 157.81)	99.75 ± 46.19 89.8 (26.37 - 190.2)	1278 ± 565 1154 (334 - 2370)
Tocilizumab IV in sJIA						
12 mg/kg IV Q2W (Study NP25737)	< 30 kg	11	10.4 (6.8 - 11.5)	59.8 ± 32.4 49.0 (25.6 - 114.7)	268.9 ± 94.9 282.4 (107.0 - 416.2)	1526 ± 465 1359 (295 - 2240)
12 mg/kg IV Q2W	< 30 kg	46	18.9 (10.0 - 29.7)	68.4 ± 29.97 65.86 (18.99 - 135.48)	273.8 ± 63.8 274.4 (148.8 - 443.96)	1721 ± 505 1734 (840 - 2712)
8 mg/kg IV Q2W	≥ 30 kg	43	42.3 (30.6 - 112.7)	69.74 ± 29.1 70.73 (5.26 - 126.62)	255.8 ± 60.77 253.0 (119.58 - 404.34)	1662 ± 504 1631 (526 - 2779)

SD = standard deviation.

Figure 3: Study NP25737 Model-predicted steady-state minimum plasma concentration for patients showing the proposed 10.0 kg body weight cut-off for systemic juvenile idiopathic arthritis patients aged 1 to 2 years



Circles indicate sJIA patients aged < 2 years with predicted steady state C_{min} < 200 µg/mL.

Pharmacodynamics

Study WA28118

PD endpoints included IL-6, sIL-6R levels, CRP, ESR and incidence of anti-tocilizumab antibodies. Results were consistent with the known mechanism of action of tocilizumab. Median IL-6 levels for tocilizumab naïve patients rose after the initial dose and fluctuated through Week 12 before stabilising for both the 162 mg Q2W and 162 mg QW regimens. A similar trend was seen for prior tocilizumab patients receiving 162 mg Q2W but remained low in the 162 mg QW patients. The fluctuations were greatest for the 3 tocilizumab naïve patients who received the 162 mg Q10D regimen.

Median sIL-6R levels for tocilizumab naïve patients increased after the initial dose through Week 12 and remained relatively stable for the 162 mg Q2W regimen with lower more variable levels for the 162 mg QW through Week 52. For prior tocilizumab patients median sIL-6R levels remained relatively stable throughout the study. The largest variability was seen in for the 162 mg Q10D regimen.

The observed reduction in CRP and ESR with tocilizumab SC were similar for both BW groups and are consistent with the PD effects reported in clinical studies of tocilizumab in RA.

Efficacy

Study WA28118

The key efficacy outcomes in this study, JADAS-71, inactive disease, clinical remission, and CHAQ-DI, were exploratory only. The median and mean JADAS-71 scores generally improved (decreased) over the course of the study in tocilizumab naïve patients irrespective of BW (median decrease of -13.90 for patients weighing < 30 kg and -12.40 for weighing ≥ 30 kg), and were maintained at low scores / further decreased in prior tocilizumab patients (median decrease of -0.70 for patients weighing < 30 kg and -0.15 for weighing ≥ 30 kg).

The proportion of patients with inactive disease generally increased during the course of the study in all patients. The proportion of patients who achieved clinical remission generally increased during the course of the study in all patients.

In tocilizumab naïve patients, improvements in mean CHAQ-DI scores from Baseline to Week 52 were observed. In prior tocilizumab patients, improvements in mean CHAQ-DI scores in the ≥ 30 kg BW group, while for the < 30 kg BW group, the mean CHAQ-DI scores fluctuated around the relatively low baseline value but also decreased by Week 52.

At Baseline, the mean height standard deviation score (SDS) for the tocilizumab naïve patients in the < 30 kg BW group was below the normal reference range with smaller differences in the other three subgroups. Improvement in mean height SDS was seen in tocilizumab naïve patients in the < 30 kg BW group, while the other groups demonstrated either minor improvement or remained stable.

There were 3 patients aged 1 to 2 years at Baseline, and one patient aged ≥ 2 years but < 10.0 kg. All 3 patients aged 1 to 2 years were prior tocilizumab patients, and had been receiving tocilizumab IV for the treatment of sJIA (commercially available, off-label) and switched to tocilizumab SC at Baseline. They all entered the study with low JADAS-71 scores (0 to 1.0) and maintained or improved these scores through Week 52. The patient who was ≥ 2 years but < 10.0 kg at Baseline was tocilizumab naïve, and entered the study with high disease activity (JADAS-71 of 12.0). This decreased rapidly on tocilizumab SC treatment to minimal disease activity (JADAS-71 < 3.8) by Week 4, and inactive disease (JADAS-71 < 1.0) from Week 8 to Week 52.

Study WA29231 (long-term extension)

Study WA29231 is an ongoing, open-label safety and efficacy study that enrolled patients from Study WA28117 (pJIA) and Study WA28118 in sJIA. No clinical study report has been provided for evaluation. Only data from patients with sJIA were summarised and presented.

Thirty-eight patients (19 each from the < 30 kg and ≥ 30 kg BW groups) provided additional median treatment durations for tocilizumab SC of 0.31 years and 2.30 years, respectively. In general, the results seen at Baseline were maintained for the additional 16 or 128 weeks for the BW < 30 kg and ≥ 30 kg groups, respectively.

Analyses performed across trials

Efficacy results from Study WA28118 were compared with the pivotal tocilizumab IV Study WA18221. Only tocilizumab naïve patients were used in the comparison. JADAS-71 was analysed *post-hoc* for Study WA18221. A reduction in median JADAS-71 was seen for all patients, with a similar pattern of initial and sustained response up to Week 52 in both the tocilizumab SC and tocilizumab IV groups. Baseline median JADAS-71 was lower in the tocilizumab SC patients compared with the tocilizumab IV patients in both BW groups (15.10 versus 33.75 for BW < 30 kg, and 13.20 versus 33.25 for BW ≥ 30 kg) and remained lower at Week 52 (0.30 versus 1.60 for BW < 30 kg, and 0.20 versus 3.20 for BW ≥ 30 kg). The scores at Week 52 were consistent with inactive disease threshold (< 1.0) or minimal disease activity threshold (< 3.8).

Mean pain Visual Analogue Scale (VAS);⁶ results decreased in a similar pattern for both tocilizumab SC and tocilizumab IV patients, starting from a lower baseline value in the tocilizumab SC patients.

Mean CHAQ-DI scores showed progressive improvements from Baseline through Week 52 for both the tocilizumab SC and tocilizumab IV patients in both BW groups.

Mean height SDS values at Baseline in the tocilizumab naïve SC patients were closer to the reference value (0) than those in tocilizumab IV patients. Mean height SDS improved for

⁶ The Visual Analogue Scale (VAS) is a psychometric response scale for characteristics or attitudes that range across a continuum of values and cannot easily be directly measured, such as pain, mood and appetite. The VAS Pain Scale ranges along a 10 cm line from 'no pain' (0 cm) to 'worst pain' (10 cm), and patients mark a line at a point along the scale to indicate how they are feeling.

the tocilizumab SC patients < 30 kg and for tocilizumab IV patients in both BW groups. tocilizumab SC patients ≥ 30 kg had relatively stable mean height SDS through Week 52.

Safety

Study WA28118

A total of 51 paediatric patients were exposed to tocilizumab SC dosing. The median treatment duration was 1.0 years. AEs were experienced by 98% (50 out of 51) patients (100.0% of the < 30 kg group and 96.2% of the ≥ 30 kg group). There were some differences in AE profile by prior tocilizumab exposure and by BW group. A higher proportion of patients in the prior tocilizumab group reported upper respiratory tract infections (URTI) (15.4% versus 28.0%), sinusitis (0% versus 12.0%), pyrexia (3.8% versus 16.0%), injection site reaction, injection site swelling (both 0% versus 12.0%), and constipation (0% versus 12.0%). A higher proportion of patients in the tocilizumab naïve group reported cough (30.8% versus 16.0%), rhinorrhoea (11.5% versus 0%), and rash (26.9% versus 4.0%).

A higher proportion of patients in the < 30 kg BW group reported viral URTI (32.0% versus 19.2%, < 30 kg versus ≥ 30 kg respectively), hand foot and mouth disease (16.0% versus 0%), and viral gastroenteritis (12.0% versus 0%) compared with the patients in the ≥ 30 kg BW group. A higher proportion of patients in the ≥ 30 kg BW group reported ear infection, pharyngitis, sinusitis, injection site reaction, injection site swelling, ligament sprain (all 0% versus 11.5%, < 30 kg versus ≥ 30 kg respectively), injection site erythema (4.0% versus 34.6%), injection site pain (4.0% versus 19.2%), injection site pruritus (0% versus 23.1%), vomiting (12.0% versus 23.1%), neutropenia (20.0% versus 30.8%), leukopenia (4.0% versus 19.2%), and headache (0% versus 23.1%) compared with the patients in the < 30 kg BW group.

The majority of patients (72.5%) in the 'All tocilizumab' group experienced events of Grade 1 or 2 maximum intensity. Ten patients had Grade 3 or 4 severity events and 2 patients had Grade 5 events (sepsis and pulmonary haemorrhage).

There were 33 events of neutropaenia and 3 patients experienced 4 potential hypersensitivity reactions (hypersensitivity, platelet count decreased, pruritus, and pyrexia). There were no serious hypersensitivity events, and no hypersensitivity events leading to withdrawal. Injection site reactions (ISR) occurred in 21 patients overall (5 (20%) in the BW < 30 kg group, 16 (61.5%) in the BW ≥ 30 kg group) with 136 events. Four patients in the ≥ 30 kg BW group reported the majority (66%) of ISRs.

Two patients died during the study, both in the BW < 30 kg group. One patient died from pulmonary haemorrhage on Day 15 and 1 died from sepsis on Day 262. Both AEs leading to death were considered related to study treatment.

Seven patients (13.7%) experienced 9 serious adverse events (SAE) during the study, 5 in the BW < 30 kg group and 2 in the BW ≥ 30 kg group. Two patients (3.9%), one in each BW group, had a total of 4 AEs that led to withdrawal from study treatment. Thirteen patients had 28 events that led to dose interruption (7 patients (18 events) in the < 30 kg group and 6 patients (10 events) in the ≥ 30 kg group). Neutropaenia was the most common reason for dose interruption.

In patients < 2 years old, 2 of the 3 patients experienced Grade 3 low neutrophil counts when still < 2 years of age. Both events resolved following temporary interruption of tocilizumab, and were not associated with any serious infections. Two patients experienced Grade 3 laboratory abnormalities (low neutrophil count, elevated alanine aminotransferase (ALT)) and one patient experienced an SAE (abscess soft tissue) after they had reached > 2 years of age. Both laboratory abnormalities were managed with dose interruption, and had no clinical consequences. The SAE resolved without sequelae. The

patient aged > 2 years with a BW < 10 kg at Baseline experienced no serious or Grade 3 AEs or laboratory abnormalities during the study.

Analyses performed across trials

An analysis was performed across Studies WA28118, WA18221 and WA29231. Study WA18221 is a LTE 'All tocilizumab' IV safety population that includes safety data from 112 sJIA patients who received at least one dose of tocilizumab IV. Study WA29231 is an ongoing extension study including patients from Study WA28118 and WA28117 (pJIA) and included 38 sJIA patients.

The overall proportion of AEs was comparable in Study WA28118 (98.0%) and Study WA18221 (98.2%), with a similar proportion of AEs seen in both BW groups. The proportion of AEs was lower in Study WA29231 (73.0%). The highest rate of AEs per 100 patient years (PY) was observed in Study WA28118, which was largely driven by a higher rate of ISRs. Other commonly reported AEs included viral URTI, neutropaenia, and cough, which were all observed at a higher rate in the tocilizumab SC population compared with the tocilizumab IV population.

A numerically higher death rate was observed in the Study WA28118 All tocilizumab SC safety population (4.3 (95% confidence interval (CI): 0.5, 15.5) deaths per 100 PY) compared with the Study WA18221 LTE All tocilizumab IV safety population (0.8 (95% CI: 0.0, 4.2) deaths per 100 PY). However, there were only a small number of events resulting in wide CIs, and a large difference in cumulative PYs of exposure so it is difficult to interpret these results.

ISRs were more common following tocilizumab SC in sJIA patients (291.0 per 100 PY) than in pJIA patients (113.0 per 100 PY) and adult RA patients (30.1 and 33.6 per 100 PY). The higher frequency of injections in sJIA compared with pJIA may account for some of the observed increase in ISR rate, as in both indications ISR rates were higher in the ≥ 30 kg groups. All the ISRs in the sJIA tocilizumab SC program were non-serious, the majority were Grade 1 events, and none required study withdrawal or dose interruption.

For other AEs of special interest, some rates were higher with tocilizumab SC than tocilizumab IV (for example, neutropaenia, increased lipid parameters), some were lower (for example, hypersensitivity), and others were generally comparable (for example, infections and serious infections). Despite these differences, the overall safety profile of tocilizumab SC was comparable to that of tocilizumab IV in the sJIA population and no new or unexpected safety signals were observed.

Safety in patients aged 1 to 2 years or < 10 kg in Study WA28118 appeared to be consistent with the older patients in the study, albeit based on a very small number of patients (n = 4).

Clinical evaluator's recommendation

The clinical evaluator has recommended approval for the proposed indication.

Risk management plan

In support of the proposed SC route of administration for the sJIA indication, the sponsor has submitted European Union-risk management plan (EU-RMP) version 24.1 (dated 14 August 2018; data lock point (DLP) July 2018) and Australian specific Annex (ASA) version 10.0 (dated November 2018). Following the second round evaluation the sponsor submitted updated EU-RMP version 25.3 (5 September 2019; DLP August 2019) and updated ASA version 11.0 (dated 22 October 2019).

The sponsor has proposed routine pharmacovigilance for all safety concerns and specific adverse event follow-up forms for all safety concerns except for immunogenicity. Additional pharmacovigilance studies conducted outside Australia have been proposed to investigate general safety profile, including effects in children and in pregnancy. These activities are consistent with the previously approved risk management plan (RMP).

The sponsor has committed to implementing a health care professional brochure, a dosing guide and a patient brochure to address the important identified risk of serious hypersensitivity reactions in Australia. The sponsor has committed to providing copies for review prior to approval.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5.⁷

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Serious infection	✓*	✓†	✓	-
	Complications of diverticulitis	✓*	✓†	✓	-
	Serious hypersensitivity reactions	✓*	✓†	✓	§
	Neutropenia	✓*	✓†‡	✓	-
	Hepatotoxicity	✓*	✓†‡	✓	§+
Important potential risks	Thrombocytopenia and the potential risk of bleeding	✓*	✓†‡	✓	-
	Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity	✓*	✓†‡	✓	-
	Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events	✓*	✓†	✓	-
	Malignancies	✓*	✓†	✓	-

⁷ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

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

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
	Demyelinating disorders	✓*	✓†	✓	-
	Immunogenicity	-	-	✓	-
Missing information	None	-	-	-	-

* Specific adverse event follow-up form. † EU registry studies. ‡ Paediatric Study WA28029 (ARTHUR trial). § Healthcare professional (HCP) brochure, dosing guide and patient brochure. + HCP letter.

Risk-benefit analysis

Delegate's considerations

The sponsor proposes to extend the use of Actemra in sJIA to include SC dosing and to decrease the lower age limit to 1 year of age for the SC formulation. A PK/PD bridging study was provided to support the extrapolation of efficacy and safety for the IV tocilizumab dosing regimen to the SC tocilizumab dosing regimen. The Delegate considers the extrapolation of efficacy and safety from the IV to the SC dosing regimen to be reasonable for patients aged 2 years and above, given the comparable PK data for $C_{min,ss}$.

The Delegate is concerned that there is limited observed data available to support extrapolation of efficacy and safety for patients in the 1 to 2 year age group particularly given that IV tocilizumab is not approved for use in sJIA patients in this age group. Observed PK data for the age range 1 to 2 years of age was limited to 3 patients, aged 17, 19 and 22 months at Baseline and only two out of the three patients received the proposed Q2W dosing regimen. In addition, two of the three patients had had previous exposure to IV tocilizumab.

The observed data has been supplemented with model predicted data. The simulations included 3 patients less than 2 years old, weighing 6.8 to 10.0 kg that had higher tocilizumab exposures than previously seen with SC or IV dosing. The sponsor has introduced a 10 kg body weight cut off in order to minimise the higher tocilizumab exposures following SC administration. However, there are concerns that the model may underestimate tocilizumab SC concentrations and it has been advised that the results be interpreted with caution.

SC tocilizumab has been approved in both the EU and US for sJIA but the regulators have taken different approaches to the issue of limited observed data for the 1 to 2 year age group. The European Medicines Agency (EMA) considered the PK exposures for the SC and IV regimens to be comparable for sJIA patients aged 1 to 2 years who weigh > 10.0 kg and considered the benefit risk balance to be favourable for this age group despite low patient numbers between 1 and 2 years of age. The dosing instructions in the Summary of Product Characteristics (SmPC)⁸ limit the patient population to those weighing at least 10 kg. Efficacy endpoints in Study WA28118 were exploratory only, but JADAS-71 results in patients aged 1 to 2 years or weighing < 10 kg appeared to be consistent with that in older patients. Again, interpretation of the data is limited by the small number of patients in these categories (3 patients < 2 years old and one patient over 2 years and < 10 kg). The

⁸ Summary of Product Characteristics, SmPC RoActemra (tocilizumab) 162 mg solution for injection in pre-filled syringe, last revised 17 October 2019, available from the EMA website.

FDA did not decrease the lower age limit to 1 year of age for the SC formulation, due to limited data from Study WA28118 for this age group and as a favourable benefit risk balance was not established previously for the IV Actemra dosing regimen in this patient population. The changes proposed in the Australian submission align with those approved in the EU.

The Delegate also has concerns regarding the extrapolation of safety to the 1 to 2 year age group. Whilst Study 28118 found that safety in this patient group and those < 10 kg appeared to be consistent with the older patients in the study, again this assessment was based on only a small number of patients (n = 4).

Proposed indication

The IV formulation of tocilizumab is currently approved in Australia for use in sJIA patients aged 2 years and older. The sponsor has proposed changes to the sJIA indication for tocilizumab to include SC dosing and to decrease the lower age limit for the SC formulation to 1 year of age. As outlined above the EU and the US have both approved SC tocilizumab for use in sJIA patients but the regulators had divergent opinions on decreasing the lower age limit for the SC formulation. Subject to the advice of the Advisory Committee on Medicines (ACM), the Delegate is of the view that there is a favourable risk-benefit balance for the proposed SC route of administration in sJIA for patients aged ≥ 2 years. The Delegate has concerns regarding the safety and efficacy of SC tocilizumab in the 1 to 2 year old age group and is therefore seeking the advice of the ACM.

Deficiencies of the data

As outlined above, limited observed data is available for the SC dosing regimens particularly for patients between 1 to 2 years of age (n = 3).

Conditions of registration

The RMP evaluator has proposed the following conditions of registration and the sponsor agreed to implement a health care professional brochure, a dosing guide and a patient brochure to address the risk of serious hypersensitivity reactions.

The Actemra EU-RMP (version 24.1, dated 14 August 2018, DLP July 2018), with ASA (version 10.0, dated November 2018), included with submission PM-2018-05341-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Proposed action

The Delegate had no reason to say, at the time, that the application for tocilizumab (Actemra) should not be approved for registration for SC administration for sJIA. However, they have concerns regarding the safety and efficacy of SC tocilizumab in the 1 to 2 year old age group, and is therefore seeking the advice of ACM.

Request for Advisory Committee on Medicines advice (February 2019 meeting)

1. Please comment on the evidence provided in support of the extrapolation of the efficacy of tocilizumab IV dosing to SC dosing for the sJIA indication.
2. Please comment on the evidence provided in support of lowering the lower age limit to 1 year of age for the SC route of administration for tocilizumab.
3. Please comment on the evidence provided in support of the safety of SC tocilizumab. Does the committee have any concerns regarding the safety profile in patients aged 1 to 2 years old?
4. What are the committee's views on imposing a minimum weight restriction of 10 kg for patients receiving SC tocilizumab?

Advisory Committee considerations⁹

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 considered this product to have an overall positive benefit-risk profile for the indication:

Systemic Juvenile Idiopathic Arthritis (IV and SC formulation)

Intravenous formulation

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

Subcutaneous formulation

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

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

⁹ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. *Please comment on the evidence provided in support of the extrapolation of the efficacy of tocilizumab IV dosing to SC dosing for the sJIA indication.*

The ACM was of the view that the pharmacokinetic parameters were comparable for the IV and SC dosing regimens. Therefore, the ACM advised that extrapolation of IV efficacy data to SC use is appropriate and in accord with the TGA adopted EU guidelines.

2. *Please comment on the evidence provided in support of lowering the lower age limit to 1 year of age for the SC route of administration for tocilizumab.*

The ACM noted that the source data included sJIA subjects < 30 kg and < 2 years old in Study NP25737 however, these toddlers received weight based IV dosing. The limited data available from Study WA28118 and Study NP25737 support SC use in the patients < 2 years old. The ACM advised that while the data are limited:

- Options for these children are limited;
- IV tocilizumab does not have an indication for use < 2 year of age;
- sJIA is uncommon in children < 2 years old and recruitment into studies is difficult;
- sJIA in children < 2 years old has significant morbidity and mortality;
- SC administration is generally preferred over IV in young children;
- SC tocilizumab was approved for sJIA in EU for children from age 1 year weighing at least 10 kg;
- Use, if approved, would be limited to specialised clinics and teams, including provision of the first dose in hospital, which would facilitate the management of any AEs.

In this setting, the ACM advised that physiologically, one year old and two year old children are similar and that in clinical practice they are not traditionally treated differently.

3. *Please comment on the evidence provided in support of the safety of SC tocilizumab. Does the committee have any concerns regarding the safety profile in patients aged 1 to 2 years old?*

The ACM advised that AEs largely relate to the anti-IL6 effects of tocilizumab, which are not dependant on metabolic processes. The ACM was of the view that it is reasonable to extrapolate safety from other sJIA subjects achieving similar PK profiles. The ACM noted that while patients under the age of 2 appear to have a greater exposure to SC tocilizumab, AE risk correlates poorly with exposure. The ACM was of the view that the safety of SC tocilizumab was comparable to the IV formulation, but acknowledged that this is based on very limited data.

4. *What are the committee's views on imposing a minimum weight restriction of 10 kg for patients receiving SC tocilizumab?*

The ACM advised that young children with sJIA are often unwell and underweight, and exposure appears to increase as weight decreases; as such, a 10 kg weight restriction is safe and pragmatic.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Actemra (tocilizumab rch), 400 mg/20 mL, 80 mg/4 mL, 200 mg/10 mL concentrated solution for injection vial and 162 mg/0.9 mL solution for injection pre-filled pen and pre-filled syringe, for the following extension of indications:

Subcutaneous formulation

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

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

As such, the full indications at this time were:

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 in combination with MTX in those not previously treated with MTX;

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

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

Giant cell arteritis (SC formulation only)

Actemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients;

Polyarticular juvenile idiopathic arthritis (IV and SC formulations)

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

Systemic juvenile idiopathic arthritis (IV and SC formulations)

Intravenous formulation

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

Subcutaneous formulation

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

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

Cytokine release syndrome (CRS) (IV formulation only)

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

Specific conditions of registration applying to these goods

- The Actemra EU-RMP (version 25.3, dated 5 September 2019, DLP August 2019), with ASA (version 11.0, dated 22 October 2019), included with submission PM-2018-05341-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- For all injectable products the PI must be included with the product as a package insert.

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>>.

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>