20 September 2018
EMA/742879/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0076

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American College of Rheumatology
BW	body weight
CHAQ-DI	Childhood Health Assessment Questionnaire-DisabilityIndex
CFB	change from baseline
CI	confidence interval
CSR	clinical study report
DMARD	disease-modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
ILAR	International League of Associations for Rheumatology
ITT	intent to treat
IV	Intravenous
JADAS-71	Juvenile Arthritis Disease Activity Score 71
JIA	juvenile idiopathic arthritis
LOCF	last observation carried forward
LTE	long-term extension
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
SC	subcutaneous
SCE	summary of clinical efficacy
SDS	standard deviation score
sJIA	systemic juvenile idiopathic arthritis
TCZ	tocilizumab
TNF	tumour necrosis factor
VAS	visual analog scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 12 March 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

To add the paediatric indication 'treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids' to the RoActemra 162 mg solution for injection in pre-filled syringe formulation, based on data from the Phase Ib pharmacokinetic/pharmacodynamic bridging study WA28118 (JIGSAW 118), designed to confirm the RoActemra subcutaneous dosing regimens in patients aged 1 to 17 years old with sJIA, as well as assess the safety of the RoActemra subcutaneous formulation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated accordingly.

In addition, sections 4.2, 4.8 and 5.2 of the SmPC of the RoActemra 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal RoActemra intravenous study WA18221 (TENDER), a randomised, placebo-controlled study to evaluate the effect of tocilizumab on disease response in patients with active sJIA.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0266/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0266/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0266/2015.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Roactemra (tocilizumab – TCZ) is a recombinant humanised anti-human IgG1 monoclonal antibody directed against the interleukin-6 receptor (IL-6R) that binds specifically to both soluble and membrane-bound IL-6R, thereby inhibiting IL-6-mediated signalling.

Interleukin 6 (IL-6), the ligand of IL-6R, is a cytokine produced by a wide variety of cells in the human body. Its normal role is primarily to regulate hematopoiesis, to stimulate immune responses, and to mediate acute phase reactions. Consequently, excessive production of IL-6 can be implicated in the pathogenesis of several diseases involved with these functions, such as rheumatoid arthritis (RA), multiple myeloma and Castleman's Disease. IL-6 exerts its biological effects through both the membrane bound IL-6 receptor (mIL-6R), and the soluble form of the receptor (sIL-6R). TCZ binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. TCZ has been shown to inhibit the biological activities of IL-6 in vitro and in vivo, and to suppress the development of arthritis and C-reactive protein synthesis in a collagen induced arthritis model in cynomolgus monkey.

TCZ is available in 2 different pharmaceutical forms to allow either administration by intravenous (IV) infusion or by subcutaneous (SC) injection.

In the EU, Roactemra administered by intravenous (IV) infusion or by subcutaneous (SC) injection is indicated:

- In combination with methotrexate (MTX), is indicated for:

- *the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.*
- *the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.*

In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra has been shown to reduce the rate of

progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

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

In the EU, Roactemra administered by intravenous (IV) infusion is indicated:

- in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

- 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.

In the EU, Roactemra administered by subcutaneous (SC) injection is indicated:

- for the treatment of Giant Cell Arteritis (GCA) in adult patients.

With the present application the MAH has sought an indication for Roactemra administered by subcutaneous (SC) injection for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. The MAH also proposed that RoActemra could be given alone (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

The MAH received scientific advice on the original clinical development plan for TCZ SC for the sJIA and pJIA indications on 19 January 2012 (EMEA/H/SA/860/3/2011/PED/II). The MAH has generally followed the advice given by the CHMP. The MAH designed the phase 1b study, WA28118, to bridge the proposed TCZ SC regimens to the approved TCZ IV regimens for sJIA, based on PK extrapolation. Given the unmet medical need in sJIA <2 years of age PDCO requested the MAH to extended the age range to be studied in WA28118 from >2 years to >1 year.

Background on disease

Systemic juvenile idiopathic arthritis (sJIA) is a subset of juvenile idiopathic arthritis (JIA) that is characterised by the presence of arthritis, intermittent fever, and rash. Both sexes are equally affected, with a peak incidence between the ages of 1 and 5 years, although patients with this illness are distributed throughout childhood (Ogilvie et al. 2003; De Benedetti and Schneider 2015). Diagnosis of sJIA according to the International League of Associations for Rheumatology (ILAR) criteria requires the presence of arthritis (most often polyarticular) that begins before the 16th birthday and persists for at least 6 weeks (where other known conditions are excluded) and a documented quotidian fever of at least 2 weeks' duration plus one of the following: rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, or serositis (Petty et al. 2004). In addition, the vast majority of patients will present with laboratory evidence of systemic inflammation.

Patients whose disease follows a severe, protracted course may have profound morbidity secondary to long-term treatment with glucocorticoids. Risk factors for poor outcomes include young age at diagnosis, disease duration > 5 years, persistent systemic symptoms, presence of thrombocytosis,

high erythrocyte sedimentation rate (ESR), and multiple active joints after 3 to 6 months of onset of disease.

The most severe complication of sJIA is macrophage activation syndrome (MAS), which is also known as secondary haemophagocytic lymphohistiocytosis. MAS is clinically characterized by unremitting fever, hepatosplenomegaly, lymphadenopathy, hepatic dysfunction, encephalopathy, and mucosal bleeding as well as a number of laboratory abnormalities. Severely affected patients may develop multi-organ involvement that may progress to respiratory distress, renal failure, disorientation, seizures, reduced levels of consciousness, hypotension, and shock (De Benedetti and Schneider 2015).

Within JIA, sJIA contributes about two-thirds of the total mortality rate, most of which is associated with MAS, amyloidosis, and infections related to glucocorticoid therapy (Gurion et al. 2012).

Current treatment options for sJIA include NSAIDs, steroids, and the approved biologics canakinumab (IL-1β blocker) and TCZ IV.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Tocilizumab, the pharmaceutical active ingredient in RoActemra, is a recombinant humanised immunoglobulin IgG1 monoclonal antibody produced by recombinant DNA technology. Tocilizumab is a protein with a molecular mass of approximately 145 kDa and the Chemical Abstracts Services (CAS) number 375823–41–9. Being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion, like other monoclonal antibodies, tocilizumab is unlikely to result in a significant risk to the environment. Considering human metabolism, rapid biodegradability and acute ecotoxicological properties of tocilizumab, no exposure levels of concern to the environment are to be expected. Therefore, it is considered acceptable that no formal ERA according to the EMA 2006 Guideline (corr. 2) is needed for tocilizumab.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Tabular overview of clinical studies

Study No.	Study Design	Dose and Regimen	Study Objectives	No. Patients	Status
Phase 1b PK/PD Bridging Study:					
WA28118 JIGSAW 118 (Phase 1b)	Open-label, multicenter study to investigate the PK, PD, and safety of TCZ following SC administration to patients with sJIA aged 1 to 17 years	BW < 30 kg: 162 mg TCZ SC Q10D or Q2W BW ≥ 30 kg: 162 mg TCZ SC QW	Characterize the PK, evaluate the PD and safety, and describe the efficacy (exploratory) of TCZ SC in patients with sJIA	N = 51	Completed
Supportive Studies:					
WA18221[a] TENDER (Phase 3)	Five-year, three-part study in patients with active sJIA aged 2 to 17 years Part I: 12-week, randomized, double-blind, placebo-controlled, parallel group, 2-arm phase Part II: 92-week, single-arm, open-label extension phase Part III: optional, 3-year, single-arm, open-label, long-term extension phase	Part I: BW < 30 kg: 12 mg/kg TCZ or placebo IV Q2W BW ≥ 30 kg: 8 mg/kg TCZ or placebo IV Q2W Part II: BW < 30 kg: 12 mg/kg TCZ IV Q2W BW ≥ 30 kg: 8 mg/kg TCZ IV Q2W Part III: TCZ standard dosing: Same as Part II or TCZ alternative dosing schedule, same as standard dosing but Q3W, Q4W, or no TCZ infusions	Part I: Evaluate the efficacy and short-term safety of TCZ IV versus placebo in combination with stable ongoing therapy Part II: Evaluate the safety of TCZ in chronic administration and effect of TCZ to enable the reduction or elimination of corticosteroids Part III: Assess long-term safety of TCZ in children with sJIA with regard to adverse events and laboratory abnormalities	Part I: N=112 (TCZ: 75; placebo: 37) Part II: N=112 Part III: N=89	Completed
WA29231 (Phase 1b, LTE)	LTE study for WA28118 (sJIA) and WA28117 (pJIA) to evaluate the safety and efficacy of TCZ SC in patients with sJIA[b] and pJIA (maximum 5 additional years of treatment)	For sJIA: BW < 30 kg: 162 mg TCZ SC Q10D or Q2W BW ≥ 30 kg: 162 mg TCZ SC QW	Evaluate the long-term safety and efficacy of TCZ SC in patients with sJIA[b] and pJIA	N = 38[c]	Ongoing

PK = pharmacokinetic; PD = pharmacodynamics; TCZ = tocilizumab; SC = subcutaneous; sJIA = systemic juvenile idiopathic arthritis; BW = body weight; Q10D = every 10 days; QW = every week; Q2W = every 2 weeks; IV = intravenous; sJIA = systemic juvenile idiopathic arthritis; LTE = long-term extension.

[a] Data as of 10 May 2010 (datacut) for the LTE Study WA18221 are presented in this dossier. [b] Only data from patients with sJIA are summarized in this dossier.

[c] 38 patients were enrolled by the clinical cutoff date (11 August 2017) and are included in the ITT population; 37 patients had at least one post baseline assessment and are included in the safety population.

2.3.2. Pharmacokinetics

The MAH has proposed a fixed dose of 162 mg once every 2 weeks (Q2W) for patients weighing < 30 kg and once every week (QW) for patients weighing ≥ 30 kg as an alternative to the currently licensed TCZ IV infusion.

Overview of clinical studies

The main Study WA28118 (JIGSAW 118) was designed to bridge from tocilizumab (TCZ) intravenous (IV) to TCZ subcutaneous (SC) in 1-17-year-old patients with systemic juvenile idiopathic arthritis (sJIA).The pre-filled syringe with needle safety device (PFS + NSD) approved in both the United States (US) and the European Union (EU) for the treatment of adults with rheumatoid arthritis (RA) was used in the Phase Ib bridging program for TCZ SC in sJIA.

Data from two supportive studies (WA18221 (pivotal IV study), WA29231) have been taken into account regarding this application (see Table above). Study WA29231 is an open-label extension of the TCZ SC JIGSAW studies (WA28117 (pJIA) and WA28118 (sJIA)).

Study WA28118 was a Phase Ib, 52-week, open-label, multicenter, PK/PD and safety study in paediatric patients with sJIA, aged 1 to 17 years old (12 to 17 years old for patients in Russia). The study aimed to identify the SC regimens that achieve comparable PK/PD and safety profiles to the IV regimens established in Study WA18221.
The study planned to enrol approximately 48 patients (actual N = 51), of which no more than 50% should have switched from TCZ IV to TCZ SC at baseline, who fulfilled all of the inclusion criteria, and none of the exclusion criteria. The patients received TCZ SC according to their body weight (BW), with

patients weighing ≥ 30 kg (planned N = 24, actual N = 26) receiving 162 mg TCZ SC QW, and patients weighing < 30 kg (planned N = 24, actual N = 25) receiving 162 mg TCZ SC every 10 days (Q10D) or Q2W (see change in dosing regimen post-interim analysis below) for 52 weeks. All patients weighing < 30 kg enrolled after the interim analysis (N = 17) received the Q2W dosing regimen. Eight patients weighing < 30 kg who were enrolled prior to interim analysis remained on Q10D dosing for the entire study.
Demographic and disease characteristics at baseline were as expected in this paediatric patient population and were overall well balanced between BW groups.
The two body weight groups differed in median age (5 years vs. 14 years), median height (104.5 cm vs. 154.8 cm), and median weight (19.6 kg vs. 51.7 kg), as expected for these BW dosing groups. Three patients were under the age of 2 years at baseline.

Pharmacometrics Methods

Clinical pharmacokinetics of TCZ was characterized using the population PK approach which includes 140 sJIA patients from Studies WA28118 (n = 51, SC) and WA18221 (n = 89, IV). The population PK model is a two-compartment PK model with parallel linear and Michaelis-Menten eliminations, and a first-order absorption to describe SC administration. The compartmental models were parameterized in terms of clearance(s) and volume(s) of distribution. The structural model used to describe the PK of TCZ for sJIA is the same as that used to describe the PK of TCZ in pJIA and adult RA patients.
Nonlinear mixed-effect modelling was conducted using the software NONMEM version 7.3.0.
Based on prior knowledge from the previous population PK analysis using SC and IV data from pJIA patients, the population PK model contained the following covariates: BSA on linear CL, Vp and Vm, height (HT) on Vc, and BMI on Ka and Fsc. This model was used as the starting point of the population PK analysis. Covariate effects identified for pJIA patients in the previous analysis using SC and IV data were re-evaluated and non-significant effects were removed. Additional covariate effects were also tested and not retained if their effects were not significant.

The predictive performance of the final population PK model was evaluated by graphical evaluations, precision of the parameter estimates, visual predictive check, predictive check simulations, and normalized prediction distribution errors.

A PK/PD bridging approach was applied for TCZ SC Dose Selection, taking a dosing modification after the interim analysis into account.

PK samples

A total of 832 PK samples were collected from 51 patients in Study WA28118.

Serum PK samples were obtained according to the following schedule:

- For patients weighing < 30 kg and < 2 years old on the Q10D regimen:
  Pre-dose, Day 4, 10, 30, 50, 70, 90, 90.5, and 100;
- For patients weighing < 30 kg and > 2 years old on the Q10D regimen:
  Pre-dose, Day 0.25, 0.5, 2, 4, 10, 30, 50, 70, 90, 90.25, 90.5, 91, 92, 94, 96, and 100;
- For patients weighing < 30 kg and < 2 years old on the Q2W regimen:
  Pre-dose, Day 5, 14, 42, 70, 84, 85, 88, and 98;
- For patients weighing < 30 kg and > 2 years old on the Q2W regimen:
  Pre-dose, Day 0.25, 0.5, 2, 5, 14, 42, 56, 70, 84, 84.25, 84.5, 86, 87, 88, 90, and 98;

- For patients weighing ≥ 30 kg on the QW regimen:
  Pre-dose, Day 0.25, 0.5, 2, 4, 7, 14, 28, 56, 91, 91.25, 91.5, 92, 93, 95, 96, and 98.

Overall, 3.6 % of observed concentrations were below the limit of quantification and were excluded.

The CHMP noted that the percentage of excluded BLQ samples from further analyses is 3.6% and thus in an acceptable range. The number of excluded non-BLQ samples is also deemed acceptable.

The median observed PK concentration-time profiles of TCZ following 52 weeks of treatment are shown in the Figure below. Observed pre-dose concentrations reached a stable level around Week 14 following the 162 mg Q2W (BW < 30 kg) and QW (BW ≥ 30 kg) regimens for both TCZ naive and prior TCZ patients. There was large variability in the observed TCZ concentration data especially for 3 TCZ naive patients who received the 162 mg Q10D regimen (BW <30 kg).

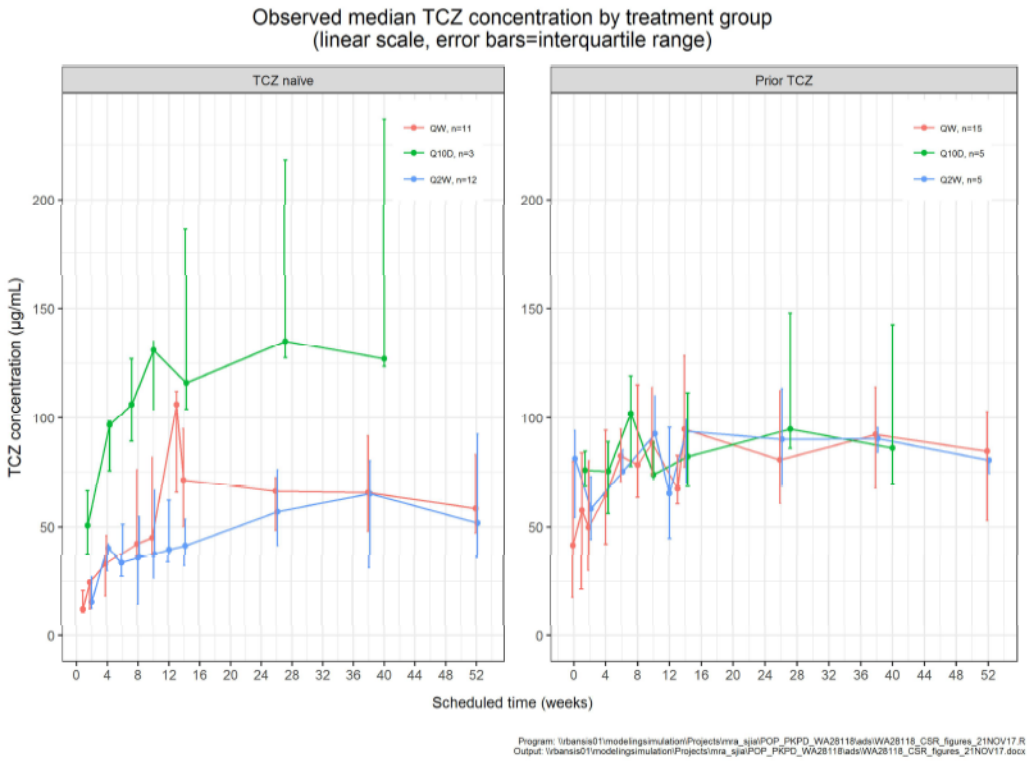


Figure 1 Observed median TCZ concentration by treatment group (linear scale, error bars = interquartile range)

A summary of observed median Cmin values by TCZ status and by BW (and dosing regimen) is provided in the Table below.

Table 2 Summary of observed median Cmin values by TCZ status and by BW (and dosing regimen)

Median C_{min} (range) in µg/mL	TCZ Naive (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)

C_{min} = minimum concentration

Following SC dosing, almost all patients had observed steady-state Cmin above the p5th achieved with TCZ IV, except for 2 patients (8%) treated with 162 mg SC Q2W (BW < 30 kg).

Population PK

The population PK database included dosing, PK, and covariate data from the Phase Ib Study WA28118 and Part I of Phase III Study WA18221. The dataset consisted of 1710 serum samples from 140 paediatric patients with sJIA (Study WA28118: n = 51, Study WA18221: n = 89).

The population PK model parameters included linear CL, inter-compartmental CL (Q), VC, VP, VM, the Michaelis-Menten constant (KM), absorption rate constant (Ka), and SC bioavailability (Fsc). Inter-subject variability was incorporated on linear CL, VC, VP, and Ka.

Final population PK parameters:

The PK parameter estimates for sJIA patients from the final population PK model are shown in the Table below.

Table 3 PK parameter estimates for sJIA patients from the final population PK model

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
CL (L/day)	θ_1	0.137	4.53	0.125–0.149		
V_C (L)	θ_2	1.87	3.24	1.75–1.99		
V_P (L)	θ_3	2.14	8.00	1.81–2.48		
V_M (mg/L/day)	θ_4	6.6	10.3	5.27–7.93		
Q (L/day)	θ_5	0.354	6.37	0.31–0.399		
K_M (µg/mL)	θ_6	4.61	36.8	1.28–7.94		
k_a (1/day)	θ_7	0.403	12.0	0.308–0.498		
F_{SC}	θ_8	0.948	2.80	0.895–1		
σ_{prop}	θ_9	0.165	3.30	0.154–0.175		
σ_{add}	θ_{10}	2.28	9.59	1.85–2.71		
η ratio	θ_{11}	1.36	13.8	0.993–1.73		
$CL,V_C,V_P,V_{M,sex}$	θ_{12}	1.1	2.91	1.04–1.16		
$CL,V_C,V_P,V_{M,BSA}$	θ_{13}	1.03	4.27	0.947–1.12		
$V_{M,SCRT}$	θ_{14}	-0.616	13.7	-0.782 – -0.45		
$k_{a,BMI}$	θ_{15}	-0.806	87.4	-2.19–0.576		
$F_{SC,BMI}$	θ_{16}	-0.795	26.9	-1.22 – -0.376		
ω^2_{CL}	Ω(1,1)	0.0442	16.5	0.03–0.0585	CV=21.0%	13.4%
ω^2_{VC}	Ω(2,2)	0.0365	20.8	0.0217–0.0514	CV=19.1%	15%
ω^2_{VP}	Ω(3,3)	0.367	14.6	0.262–0.471	CV=60.5%	15.9%
ω^2_{ka}	Ω(4,4)	0.339	28.5	0.15–0.529	CV=58.2%	9.5%
ω^2_{EPS}	Ω(5,5)	0.0545	22.5	0.0304–0.0785	CV=23.3%	14.8%
σ^2	Σ(1,1)	1	fixed	fixed	1	4.9%

CV = coefficient of variation; RSE = relative Standard Error; SE = standard error; SD = standard deviation
Note: RSE = 100·SE/PE; CV = 100*SD %.

Model evaluation

The following Figures show the goodness-of-fit plots for the final population PK Model stratified by study (and thus, by route of administration).

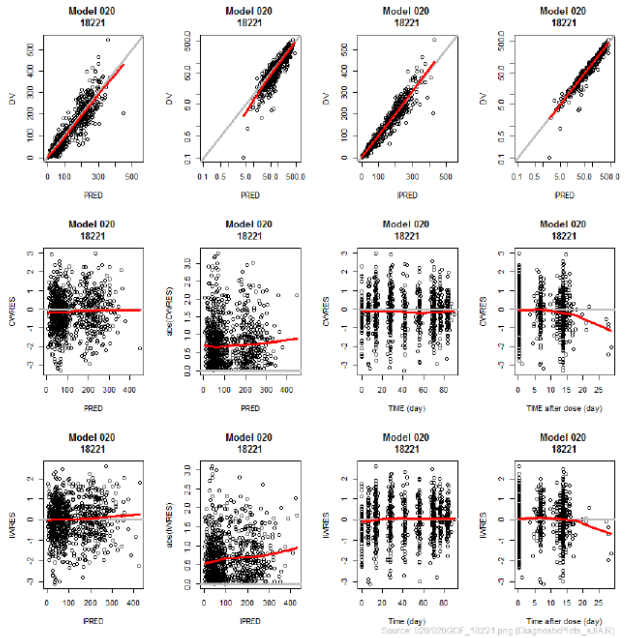
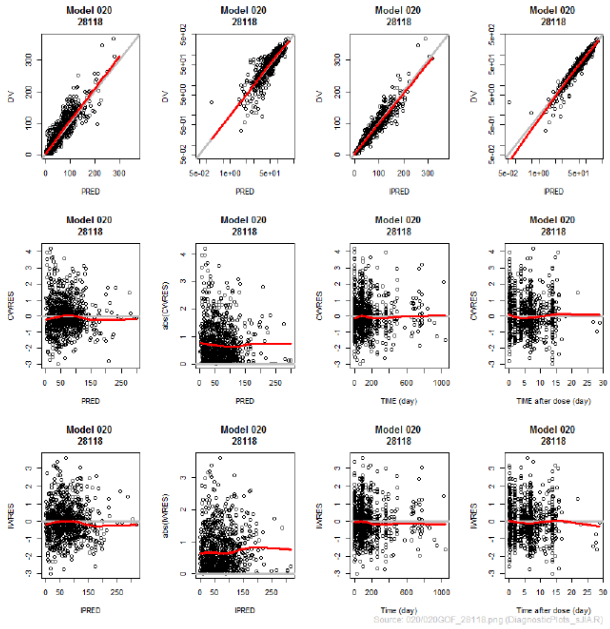
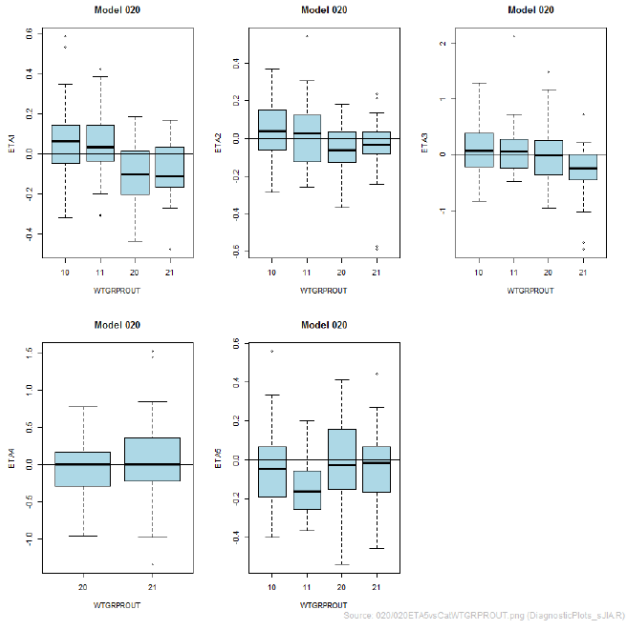
Goodness-of-Fit Model 020: Study WA18221,IV Data	Goodness-of-Fit Model 020: Study WA28118,SC Data
DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **IWRES**: individual weighted residuals; **TIME**: time after the first dose; **TAD**: time after the most recent dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines. 	**DV:** Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **IWRES**: individual weighted residuals; **TIME**: time after the first dose; **TAD**: time after the most recent dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines. 

Figure 2 Goodness-of-fit plots for the final population PK Model stratified by study

Dependencies of the random effects on route of administration and weight are depicted below.

Table 4 Relationships of the Inter-Individual Random Effects with Route of Administration and Weight Category for Model 020

The individual random effects are plotted versus covariate using box and whisker plots. Median values of the random effects are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles. Solid lines at y = 0 are included for reference. GRPROUT: identification variable for route of administration and weight (10= IV, WT < 30 kg; 11 = IV, WT ≥ 30 kg; 20 = SC, WT < 30 kg; 21 = SC, WT ≥ 30 kg). ETA1: the random effect on linear clearance (CL); ETA2: the random effect on central volume (V_C); ETA3: the random effect on peripheral volume (V_P); ETA4: the random effect on absorption rate constant (k_a); ETA5: the random effect on residual error.

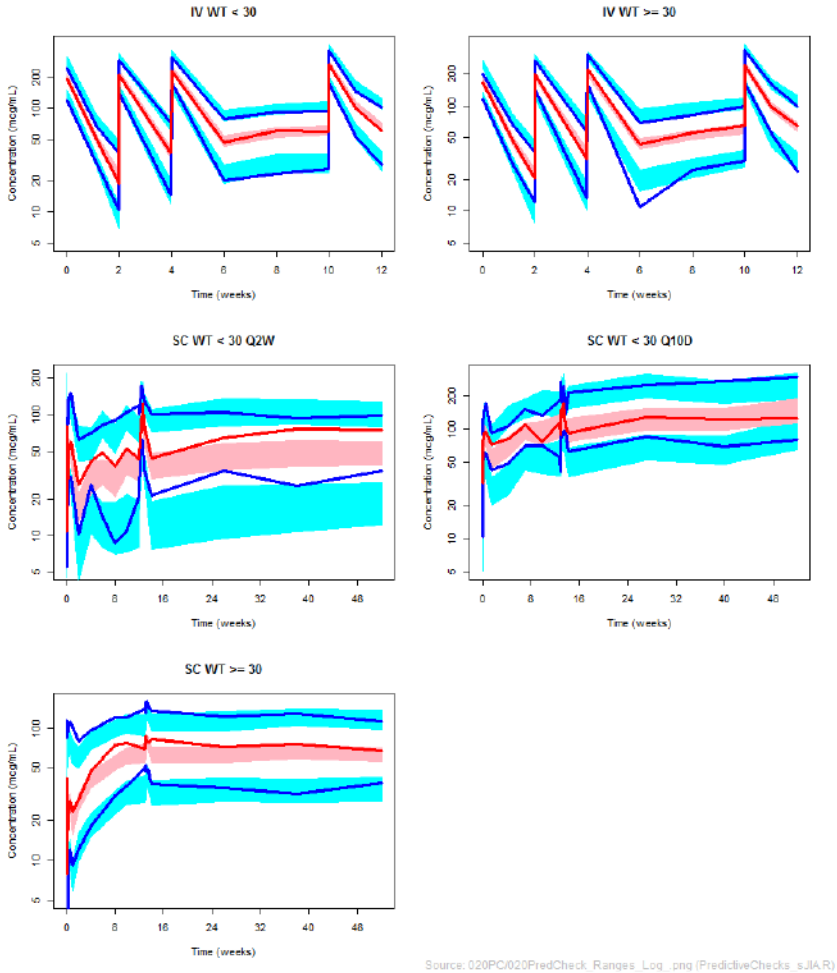


Source: 020/020ETA5vsCatWTGRPROUT.png (DiagnosticPlots_sJIA.R)

The results of the predictive check evaluation are shown below.

Table 5 Visual Predictive Check (with Confidence Intervals) for Model 020, by Route of Administration, Weight Group, and Dosing Regimen: Semi-Log Scale

The lines show median (red), and the 10th and 90th percentiles (blue) of the observed concentrations. The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.



Source: 020PC/020PredCheck_Ranges_Log_.png (PredictiveChecks_sJIA.R)

Rationale for the PK/PD Bridging Approach and TCZ SC Dose Selection

Steady-state Cmin has been established as the primary PK -parameter of efficacy and thus also for bridging between indications and formulations for TCZ. This was previously considered acceptable (Scientific Advice on TCZ SC development in sJIA - EMEA/H/SA/860/3/2011/PED/II).

Based on the population PK model developed for sJIA with the IV formulation (Study WA18221), and assuming similar SC absorption as in the adult RA population, PK profiles for different SC dose regimens were simulated for sJIA patients, with a focus on the steady-state Cmin (primary PK – parameter of efficacy). By combining this popPK model developed for the IV formulation with prior knowledge on SC absorption from the adult RA population, simulations of the SC PK profiles in sJIA patients were conducted to support the selection of the SC dosing regimens to be evaluated in the IV to SC bridging Study WA28118. Based on the simulation results, 162 mg TCZ SC Q10D (BW < 30 kg) and 162 mg TCZ SC QW (BW ≥ 30 kg) were initially recommended by the MAH for sJIA patients

because all patients were predicted to achieve a steady-state Cmin above the 5th percentile (i.e., p5th) of that achieved by the TCZ IV formulation, across the body weight spectrum for sJIA patients.

An interim analysis was planned at Week 14 to confirm that the proposed SC regimens would achieve similar steady-state Cmin compared with the approved IV regimens. At interim analysis, a higher than anticipated steady-state Cmin was achieved following the Q10D dosing regimen (BW < 30 kg), especially for the lighter patients (see Figure below). This was attributed to a higher bioavailability of TCZ SC estimated to 93.9% in sJIA patients (based on data from 28 patients available at the time of interim analysis) compared with adult RA patients (79.0%). Therefore, the initial Q10D dosing regimen for patients < 30 kg was changed to Q2W. For patients ≥ 30 kg, the steady-state Cmin were similar to that achieved following IV administration, so the QW regimen was considered adequate and was not changed.

Absorption

The bioavailability estimated by population PK analysis for a typical sJIA patient with a BMI of 18, BSA=1.25 m2, HT=1.432 m, SCRT =43 µmol/L is 94.8% (95% CI: 89.5 – 100%), which is higher compared with that estimated for adult RA patients (79.5%) and similar to that estimated for pJIA patients (96.4%)

This difference in bioavailability of TCZ SC between paediatric sJIA/pJIA and adult RA patients is likely attributed to the higher permeability of the integumentary system (skin) in paediatric patients, as developmental clinical pharmacology literature have shown that the permeability of the integumentary system is highest at infancy and converges to adult levels by adolescence.

The absorption rate constant of TCZ following SC administration was estimated by population PK analysis to 0.403 1/day (95% CI: 0.308-0.498 1/day).

Distribution

The central volume of distribution was estimated for the typical sJIA patient by population PK to 1.87 L (95% CI: 1.75 – 1.99 L). and the peripheral volume of distribution to 2.14 L (95% CI: 1.81 – 2.48 L).

Elimination

Due to dependence of total clearance on TCZ concentrations, the effective half-life of TCZ is concentration-dependent. Based on simulations, the median effective half-life of TCZ during an inter-dose interval at steady-state varies between 12.2 and 13.5 days for the 162 mg QW regimen in patients weighing ≥ 30 kg. For patients weighing < 30 kg, the median effective half-life of TCZ during an inter-dose interval at steady-state varies between 10.7 and 13.9 days for the 162 mg Q2W regimen.

Linear clearance was estimated by population PK analysis to 0.137 L/day for the typical sJIA patient with 95% CI of 0.125 to 0.149 L/day.

Special populations

Consistent with the knowledge on the PK of TCZ in other indications, body size parameters (BSA and BMI) were the most significant covariates in explaining the variability in the PK for TCZ in sJIA. BSA

was identified to have a significant impact on linear CL, Vc, Vp, and VM. BMI was identified to have a significant impact on the SC absorption parameters Ka and FSC, with decreasing Ka and FSC correlated with increasing BMI.

Similar to the previous analysis conducted for pJIA patients, serum creatinine was also identified to have an influence on the VM rate constant in sJIA. In addition, gender was identified to have a minor impact on linear CL, VC, VP, and VM. Consistent with the previous analysis conducted for pJIA patients, influences from serum creatinine and gender were not clinically significant.

The impact of the identified covariates on the typical values of PK parameters is summarized in the Table below.

Table 6 Covariate Effects Estimated by the Final Population Pharmacokinetic Model

Parameter	Covariate	Reference Value	Covariate Value [a]	Covariate Effect Value [95%CI](%)
V_C, V_P, CL,V_M	Sex	Female	Male	9.9 [3.7; 16.2]
	Body surface area	1.25 m^2	0.47 m^2	-63.6 [-66.6; -60.4]
			1.89 m^2	53.3 [47.9; 58.9]
V_M	Serum Creatinine	43 µmol/L	18 µmol/L	71 [48; 97.5]
			71 µmol/L	-26.6 [-32.4; -20.2]
k_a	Body mass index	18 kg/m^2	13.8 kg/m^2	23.9 [-14.2; 78.8]
			31.6 kg/m^2	-36.5 [-70.8; 38.3]
F_{sc}	Body mass index	18 kg/m^2	13.8 kg/m^2	5.5 [b]
			31.6 kg/m^2	-36.1 [-49.5; -19.1]

CL = clearance; F_{sc} = subcutaneous bioavailability; K_a = absorption rate constant; V_c = volume of distribution of the central compartment; V_p = volume of distribution of the peripheral compartment; V_M = maximum target-mediated elimination rate.

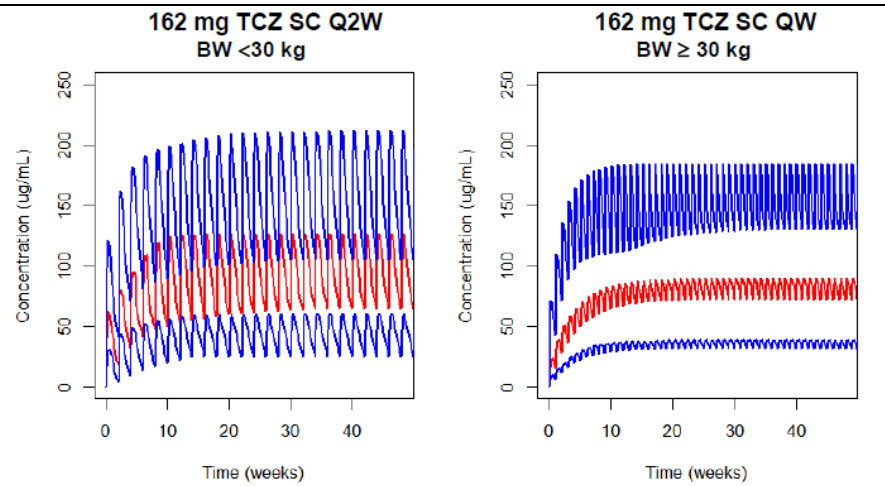
[a] The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis data set.

[b] F_{sc} values were restricted to be ≤1.

However, body size is the only covariate which has an appreciable impact on the PK of TCZ in terms of absorption, distribution and elimination.

PK in the target population

Using the individual Bayesian post hoc parameters estimated by the final population PK model, concentration-time profiles were simulated for all sJIA patients included in the population PK analysis based on per protocol dosing (see Figure below).



Median (red) and 90% prediction intervals (blue) of the simulated concentration-time profiles following 162 mg TCZ SC Q2W or QW. For each dosing regimen, concentrations were simulated for sJIA patients from Study WA28118.

Figure 3 Simulated TCZ Concentration-Time Profile by Regimen for sJIA Patients from Study WA28118

Steady-state secondary PK parameters Cmin, Cmax, and average concentration over the dosing interval (Cmean) were computed for each patient and summarized in the Table below. In order to compare the AUCss computed for the SC regimens with the IV regimens (12 mg/kg Q2W for BW < 30 kg and 8 mg/kg Q2W for BW ≥ 30 kg), AUCss,0-2weeks is computed and summarized.

Table 7 Summary of Estimated Steady-State Exposure Parameters for TCZ SC in sJIA by Regimen

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)	$AUC_{0-2\ weeks}$ (µg/mL • day) Mean ± SD Median (Min–Max)
162 mg SC Q2W BW < 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 BW ≥ 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)

AUC = area under the concentration-time curve; BW = body weight; C_{max} = maximum concentration; C_{min} = minimum concentration; QW=every week; Q2W = every 2 weeks; SC = subcutaneous; SD = standard deviation.

Following SC dosing, more than 95% of sJIA patients treated with TCZ SC had an estimated steady-state Cmin higher than the p5th achieved with TCZ IV across the spectrum of body weights. While the median steady-state Cmax was higher for patients in the < 30 kg BW group, the median and range of AUCss,0-2 weeks are similar for both BW groups.

Dose proportionality and time dependencies

Simulations of the population concentration-time profiles showed that the concentrations following the Q2W SC regimen in the < 30 kg BW group were higher overall compared with the QW SC regimen in the ≥ 30 kg BW group.

The accumulation ratios for Ctrough are 4.39 and 3.21 for the TCZ 162 mg QW and Q2W SC regimens, respectively; for AUCtau and Cmean, the accumulation ratios are 4.28 for the QW SC regimen and 2.27 for the Q2W SC regimen. Approximately 90% of the steady-state exposure levels were reached after the 6th SC injection in the Q2W regimen, and after the 12th SC injection in the QW regimen.

Comparison of Pharmacokinetics of IV and SC Administration in sJIA

More than 95% of patients (49/51) treated with TCZ SC had a steady-state Cmin above the p5th achieved with TCZ IV across the spectrum of body weights.

The median steady-state Cmin were similar between the TCZ SC and IV regimens, and the range of steady-state Cmin also largely overlapped between the SC and IV regimens as shown below.

Table 8 Comparison of Estimated Steady-State Exposure Parameters by Regimen (PK Population)

Dosing Regimen	Weight Group	n	Median BW (Min – Max) (kg)	C_{min} (µg/mL) Mean ± SD Median (Min – Max)	C_{max} (µg/mL) Mean ± SD Median (Min – Max)	$AUC_{0-2weeks}$ (µg/mL×day) Mean ± SD Median (Min – Max)
TCZ SC in sJIA						
162 mg SC Q2W	BW < 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	BW ≥ 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)
TCZ IV in sJIA						
12 mg/kg IV Q2W	BW < 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	BW ≥ 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)

Note: The corresponding SC and IV BW treatment regimens from Study WA28118 and Study WA18221 are highlighted with matching colors.
The number of TCZ IV sJIA patients includes all patients randomized to TCZ in Part I of the study as well as any patient who escaped from placebo to TCZ in Part I and had a PK sample available.
AUC = area under the concentration-time curve; BW = body weight; C_{max} = maximum concentration; C_{min} = minimum concentration; IV = intravenous; QW=every week; Q2W = every 2 weeks; SC = subcutaneous; SD = standard deviation.

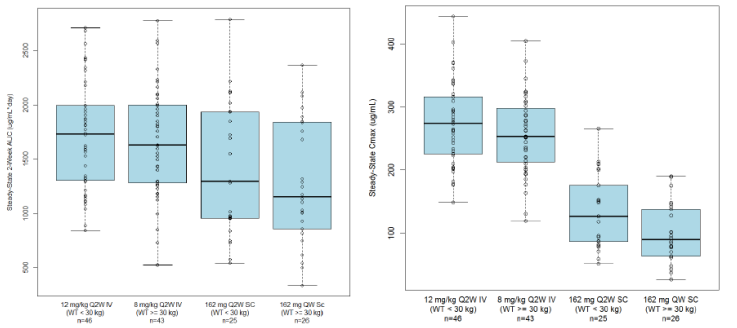
Consistent with the estimated steady state Cmin, the median and the range of observed steady-state Cmin following TCZ IV and SC were also similar and largely overlapped. Following TCZ SC administration, the median AUCss,0-2weeks achieved was lower compared with that achieved following TCZ IV administration. However, the range of AUCss,0-2weeks largely overlapped for the TCZ SC and IV regimens. As expected, the Cmax achieved by TCZ SC was much lower compared with that achieved by TCZ IV.

Table 9 Comparison of Observed Steady-State Cmin by Regimen, PK Population

Dosing Regimen	Number of Observations/Patient	Mean±SD	Median (Min–Max)
TCZ SC in sJIA (WA28118)			
162 mg SC Q2W	65/16	66.18±31.74	68.1 (4.58–135)
162 mg SC QW	93/23	80.03±38.39	74.1 (22.7–213)
TCZ IV in sJIA (WA18221)			
12 mg/kg IV Q2W	40/40	66.77±30.05	61.6 (17.8–149)
8 mg/kg IV Q2W	40/40	67.58±27.37	66.3 (5.79–120)

Note: PK population for Study WA18221 includes patients enrolled in Part 1 (12 weeks) of the study. Observed steady-state C_{min} values were defined as all observed pre-dose concentrations (non-BLQ) collected in each patient at Week 12 and onward, after starting IV or SC treatment.

Table 10 Estimated Steady-State Cmin, AUCss, 0-2w and Cmax Following SC and IV Regimens for sJIA



Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5×IQR.

2.3.3. Pharmacodynamics

Mechanism of action

Based on the known mechanism of action, TCZ binds specifically to both sIL-6R and membrane-bound IL-6R to inhibit IL-6R-mediated signalling.

Primary and secondary pharmacology

Graphical analyses were conducted to investigate the relationship between TCZ exposure and biomarkers of mechanism of action: sIL-6R and IL-6, and biomarkers of inflammation: CRP and ESR.

PD Markers

Soluble IL-6R (sIL-6R), serum IL-6, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) data for the prior TCZ patients in TCZ SC Study WA28118 have been investigated as PD Marker.

Soluble Interleukin 6 Receptor (sIL-6R)

For the TCZ naive patients, the median sIL-6R concentration increased rapidly after the first dose for both SC regimens through Week 12, after which the range of sIL-6R concentration remained relatively

stable through Week 52. As expected for the prior TCZ patients (i.e., patients who switched from commercial TCZ IV to TCZ SC at baseline), the median sIL-6R concentration remained relatively stable from the first dose up to Week 52, except at Week 52 for the prior TCZ patients with BW ≥ 30 kg. This lower observed median sIL-6R concentration may be attributed to the small patient number (n = 5) and an unusually low sIL-6R concentration at this time point observed in 2 patients. Similar to the TCZ serum concentration data, there was large variability in the observed sIL-6R concentration data, especially for the 3 TCZ naive patients who received the 162 mg Q10D regimen (BW < 30 kg).

The observed changes in sIL-6R concentration were slightly higher for patients treated with the 162 mg Q2W/Q10D (BW < 30 kg) regimen compared with patients treated with 162 mg QW (BW ≥ 30 kg), for both TCZ naive and prior TCZ patients. However, this did not translate to notable differences in downstream inflammatory biomarkers (CRP and ESR, see below). The range of sIL-6R concentrations achieved at steady-state for the SC and IV regimens was similar.

Serum Interleukin-6 (IL-6)

Serum interleukin 6 (IL-6) concentration levels increased rapidly following the first dose for all TCZ naive patients and fluctuated slightly between doses through Week 14 for both BW regimens. For prior TCZ patients, a similar trend was also observed for the 162 mg Q2W (BW < 30 kg) regimen, while the median concentrations for the 162 mg QW (BW ≥ 30 kg) regimen remained low.
Subsequently, the median IL-6 concentrations from Week 14 through Week 52 were similar for patients across the entire range of body weights and TCZ status. There was large variability in the observed IL-6 concentration data, especially for the 3 TCZ naïve patients who received the 162 mg Q10D regimen (BW < 30 kg).

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)

CRP and ESR concentration levels declined rapidly in TCZ-naïve patients following SC administration and remained low throughout the course of treatment from Week 4 through Week 52. For prior TCZ patients, median CRP and ESR concentration levels remained low from the first TCZ SC dose up to Week 52.

The responses in CRP and ESR concentration levels across time were comparable between the two SC BW regimens for both TCZ naive and prior TCZ patients and were also similar to that observed with the IV regimens for patients across the entire range of body weights.

Immunogenicity

In Study WA28118, the Exposure-ADA relationship cannot be characterized or evaluated because all PK-evaluable patients were ADA negative after baseline.

In study WA29231, of the 37 patients in Study WA29231, no patient was ADA positive at baseline or at any post-baseline assessment.

In the TCZ IV Study WA18221 LTE, all 112 patients were tested for ADA in a screening assay. Post-baseline, 2/112 patients (1.8%) in the All TCZ IV group, both in the < 30 kg BW group (12 mg/kg), had a positive post-baseline confirmation assay as well as a positive post-baseline neutralizing assay.

2.3.4. PK/PD modelling

Graphical exposure-response analyses were performed to assess the relationship between TCZ exposure and efficacy/safety in sJIA patients treated with the SC regimens. For each type of event

analyzed, the steady-state Cmin computed for each patient was used as the surrogate for exposure. Logistic regressions were used to investigate the exposure-response relationships between exposure and the PD parameters selected, and the Chi-square statistic was used (SAS 9.3 TS).

Exposure-Efficacy Relationship

Regarding exposure-efficacy analyses were related to PK marker Cmin. These relationships could be explained by the mechanism of action of TCZ. The effect of TCZ is known to depend on the extent and duration of the saturation of the IL-6R (as determined by the PD effects on soluble IL-6R (sIL-6R) and CRP), and the TCZ Cmin level at steady state, which represents the level of serum concentration just before the following administration, has been shown to be an adequate marker of the extent and duration of this saturation. As such, bridging between the IV and SC TCZ formulations is based on the exposure of TCZ, specifically Cmin that has previously been considered acceptable (Scientific Advice EMEA/H/SA/860/3/2011/PED/II).

Exploratory exposure-efficacy analyses were conducted for sJIA patients included in Study WA28118 to investigate the exposure-efficacy relationships following TCZ SC administration using graphical analyses for the following efficacy parameters JADAS-71 and CHAQ-DI score. The individual profiles of these measures, as well as percent change from baseline over time, were superimposed and compared for patients by regimen and by TCZ status.

To assess the exposure-efficacy relationship for TCZ naive patients, the percent change in JADAS-71 and CHAQ-DI were compared by BW group and by exposure category. In addition, the exposure-efficacy relationships for the combined BW groups in TCZ naive patients were assessed by comparing the percent change in JADAS-71 and CHAQ-DI by exposure tertiles.

Juvenile Arthritis Disease Activity Score 71 (JADAS-71)

JADAS-71 decreased over time for both TCZ naive and prior TCZ patients treated with the Q10D/Q2W and QW regimen.
Comparing the percent change in JADAS-71 for TCZ naive patients by BW group and by exposure category, there was no clear trend between exposure and reduction in disease activity (JADAS-71). For patients treated with the Q10D/Q2W regimen (BW < 30 kg), there was a trend for a greater decrease in JADAS-71 in the high versus the low exposure category. However, conversely, a trend with greater decreases in JADAS-71 was observed for patients treated with the QW regimen (BW ≥ 30 kg) in the low versus high exposure category (see Figure below).

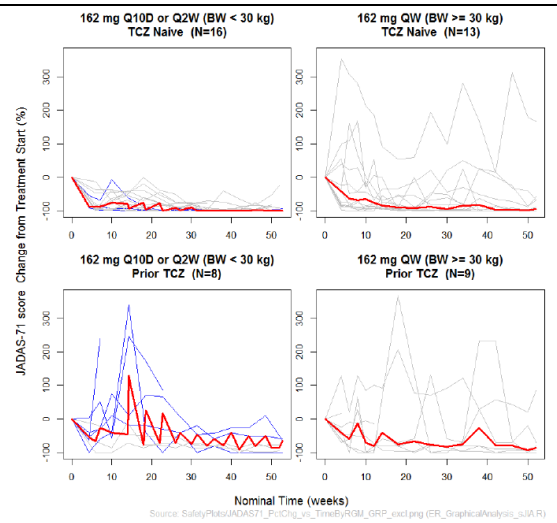
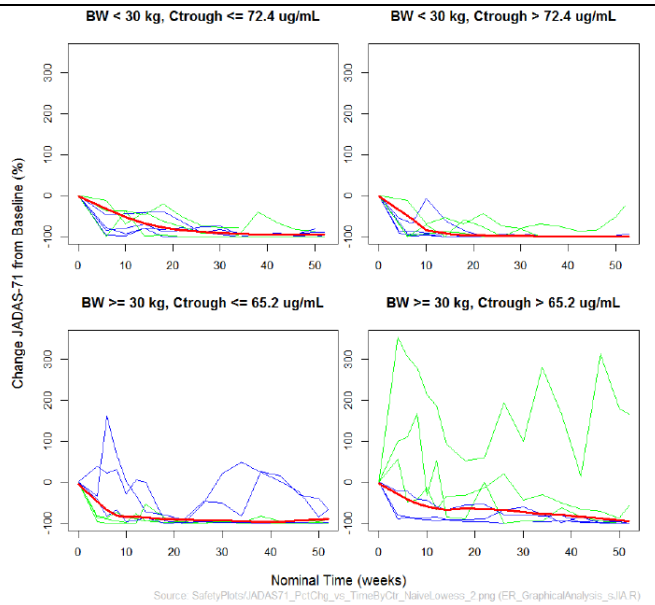
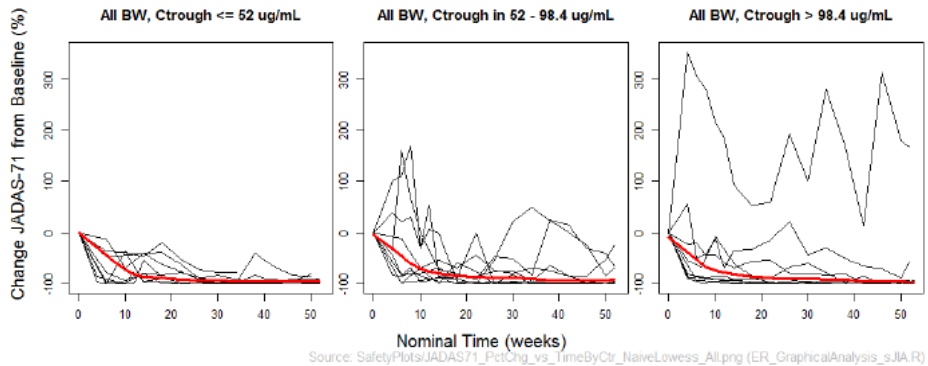
Percent Change in JADAS-71 from Baseline by Regimen and by TCZ Status (WA28118)	Percent Change in JADAS-71 from Baseline by BW Group and by Exposure Category for TCZ Naive Patients (WA28118)
 Observed change from treatment start over time (thin lines) for patients in Q10D/Q2W (left) or QW (right) TCZ dosing regimens who were TCZ naive (top) or had received TCZ previously (bottom). Red bold lines are medians. Blue lines denote patients who received the Q10D regimen. Baseline JADAS-71 was not available for 5 patients, and therefore they were not included in the graphs shown above.	 Observed change from treatment start over time for patients in Q10D/Q2W (top) or QW (bottom) TCZ dosing regimens who were TCZ naive. In each graph above, patients shown in green had steady-state C_{min} below the median of that particular category; patients shown in blue had steady-state C_{min} above the median of that particular category. Red bold lines are median percent change from baseline in JADAS-71.

Figure 4 Percent Change in JADAS-71 from Baseline

When comparing the median percent change in JADAS-71 by exposure category for all TCZ naive patients following SC administration, similar decreases in JADAS-71 were observed across the three exposure categories (see Figure below).



Red bold lines are medians.

Figure 5 Percent Change in JADAS-71 from Baseline by Exposure Category for All TCZ Naive Patients (WA28118)

Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI)

Analogously, CHAQ-DI scores decreased over time for both TCZ naive and prior TCZ patients treated with the Q10D/Q2W and QW regimen. Comparing the percent change in CHAQ-DI score by BW group and by exposure category for TCZ naive patients, there was no clear relationship between exposure

and improved physical function (reduction in CHAQ-DI score). Similar decreases in CHAQ-DI score were observed in both exposure categories for patients treated with the QW regimen (BW ≥30 kg), and a greater decrease in CHAQ-DI score were observed for patients treated with the Q10D/Q2W regimen (BW < 30 kg) in the lower exposure category (see Figures below).

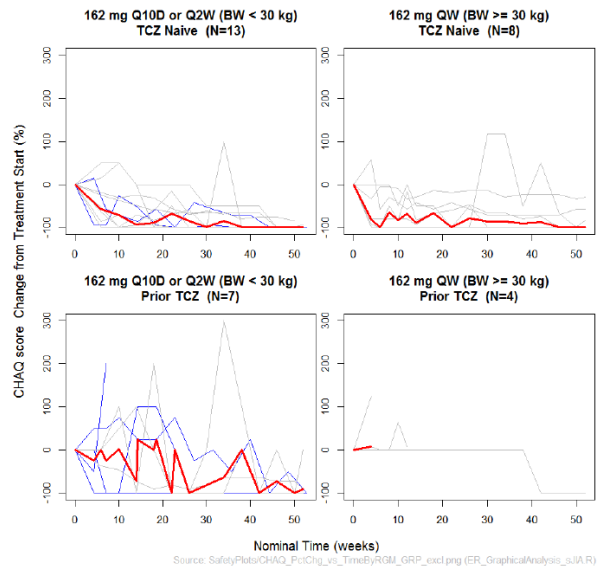
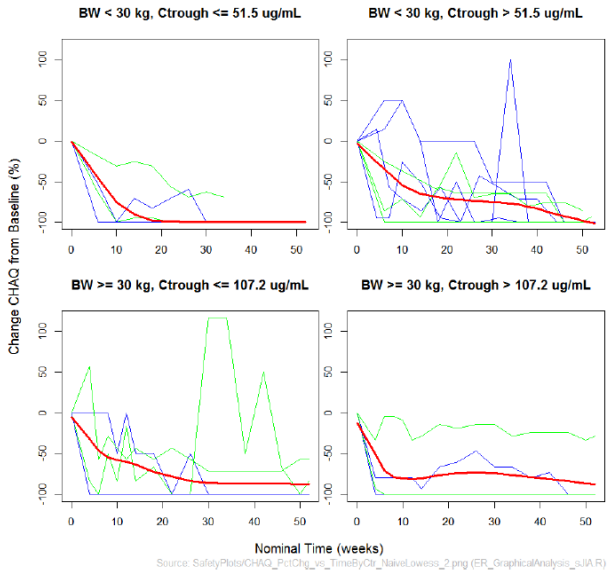
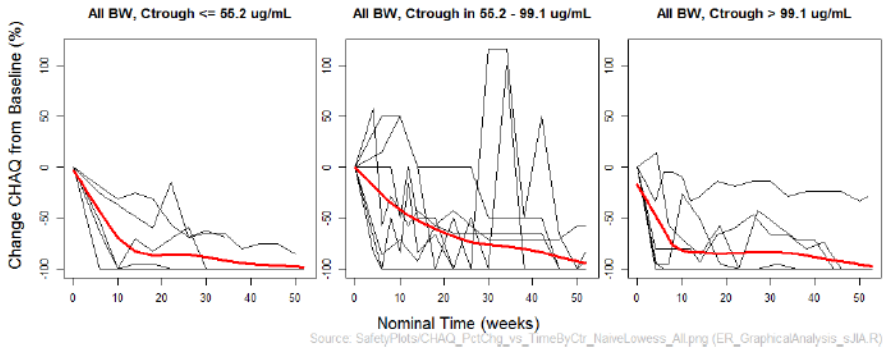
Percent Change in CHAQ-DI Score from Baseline by Regimen and by TCZ Status (WA28118)	Percent Change in CHAQ-DI Score from Baseline by BW Group and by Exposure Category for TCZ Naive Patients (WA28118)
 Observed change from treatment start over time (thin lines) for patients in Q10D/Q2W (left) or QW (right) TCZ dosing regimens who are TCZ naive (top) or received TCZ previously (bottom). Red bold lines are medians. Blue lines denote patients who received the Q10D regimen. Baseline CHAQ-DI scores were zero for 19 patients, and therefore they were not included in the graphs shown above.	 Observed change from treatment start over time for patients in Q10D/Q2W (top) or QW (bottom) TCZ dosing regimens who were TCZ naive. In each graph above, patients shown in green had steady-state C_{min} below the median of that particular category; patients shown in blue had steady-state C_{min} above the median of that particular category. Red bold lines are median percent change from baseline in CHAQ-DI. Baseline CHAQ-DI scores were zero for 19 patients, and therefore they were not included in the graphs shown above.

Figure 6 Percent Change in CHAQ-DI Score from Baseline

When comparing the percent change in CHAQ-DI score by exposure category for all TCZ naive patients, a similar trend in CHAQ-DI scores across time was observed across the three exposure categories as depicted below.



Red bold lines are medians.

Figure 7 Percent Change in CHAQ-DI Score from Baseline by Exposure Category for TCZ Naive Patients (WA28118)

Exposure-Safety Relationship

Graphical analyses were used to investigate whether the occurrence of SAEs, any AE, any AE CTC Grade 3 or above, AEs of Infections and Infestations SOC, AEs of neutropenia, and low neutrophil count laboratory abnormalities could be attributed to the variability in TCZ exposure following SC administration in Study WA28118 (n = 51).

Serious Adverse Events

A total of 7 patients (13.7%) experienced 9 SAEs during the study. In the < 30 kg BW group, 5 patients experienced 7 SAEs, 4 of which were considered related to study drug by the investigator (see also section 2.5). Of the 5 patients who experienced SAEs in the < 30 kg BW group, 4 patients were treated with the Q2W regimen and 1 with the Q10D regimen. In the ≥ 30 kg BW group, 2 patients experienced 2 SAEs, one of which was considered related to study treatment by the investigator.

Two patients in the < 30 kg BW group had a Grade 5 (fatal) SAE. One patient had a Grade 5 fatal SAE of sepsis on Day 262. The second patient had a Grade 2 SAE of oral candidiasis, a Grade 4 SAE of pneumonia, and a Grade 5 fatal SAE of pulmonary haemorrhage. Results from the logistic regression analysis showed no relationship between TCZ exposure and SAEs; however, there were a limited number of sJIA patients (n = 7) with SAEs.

Any AE (Any Grade), AEs (Grade ≥ 3), and AEs of Infections and Infestations SOC

Results from the logistic regression analysis showed no relationship between TCZ exposure (Cmin) and safety parameters mentioned (see below).

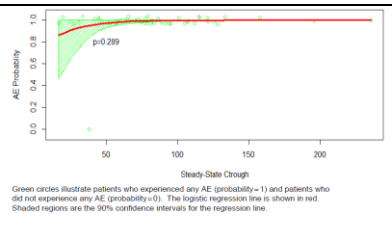
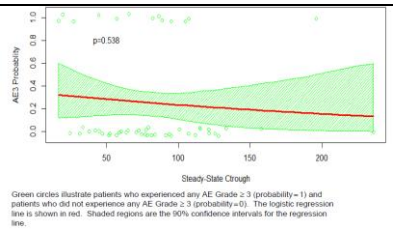
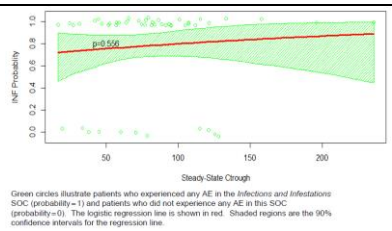
Probability of Any AE (Any Grade) versus TCZ Cmin (Study WA28118)	Probability of Any AE Grade ≥3 versus TCZ Cmin (Study WA28118)	Probability of Infections and Infestations SOC versus TCZ Cmin (Study WA28118)
		

Figure 8 Any AE (Any Grade), AEs (Grade ⩾ 3), and AEs of Infections and Infestations SOC

Neutropenia AEs and Low Neutrophil Count Laboratory Abnormalities

Overall, 13 patients experienced 33 incidents of neutropenia reported as AEs during the study. Five of the 13 patients experiencing neutropenia AEs had a BW < 30 kg, and 6 patients were TCZ naive. All neutropenia AEs except one were deemed related to study treatment, but none were considered serious. There were no serious infections within 15 days, preceding or following, a neutropenia AE.

A total of 28 patients experienced low neutrophil count laboratory abnormalities: 3 patients (5.9%) with Grade 1, 13 (25.5%) with Grade 2, and 12 (23.5%) with Grade 3. There were no patients with Grade 4 low neutrophil counts. Overall, the proportion of patients with low neutrophil count abnormalities was lower in the < 30 kg BW group (48.0%) compared with the ≥ 30 kg BW group (61.5%).

Based on logistic regression analyses, there was no relationship between TCZ exposure and neutropenia AEs of any grade, and low neutrophil count laboratory abnormalities of any grade (see below).

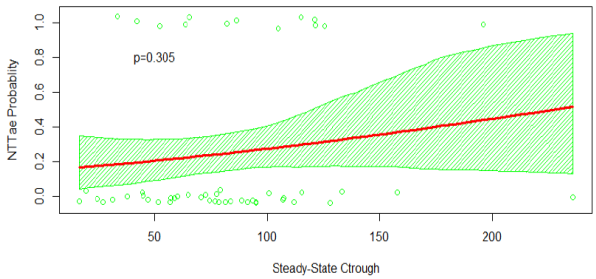
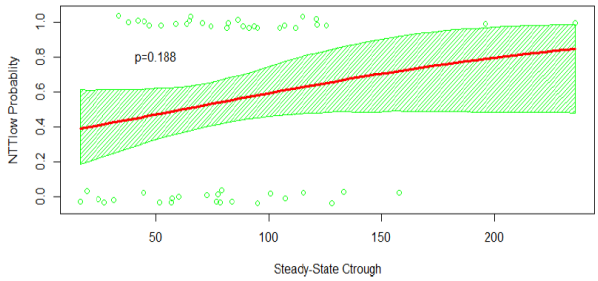
Probability of Neutropenia AEs versus TCZ Exposure (Study WA28118)	Probability of Low Neutrophil Count Laboratory Abnormalities versus TCZ Exposure (Study WA28118)
 Green circles illustrate patients who experienced any neutropenia AE of any grade (probability=1) and patients who did not experience any neutropenia AE (probability=0). The red line is the logistic regression line. Shaded regions are the 90% confidence intervals for the regression line.	 Green circles illustrate patients who experienced any low neutrophil count abnormality of any grade (probability=1) and patients who did not experience any low neutrophil count abnormality (probability=0). The red line is the logistic regression line. Shaded regions are the 90% confidence intervals for the regression line.

Figure 9 Neutropenia AEs and Low Neutrophil Count Laboratory Abnormalities

sJIA patients aged 1-2 years

Study NP25737 was a phase I study which investigated the PK, safety and exploratory PD and efficacy of TCZ IV (12 mg/kg Q2W) in the treatment of sJIA patients aged <2 years. A total of 11 patients were recruited into the study, of which 9 were aged between 1-2 years at Baseline, and 2 were aged < 1 year.

As in JIGSAW-118, the majority of these patients had BWs well within the normal range for their age and gender (between 25th-75th percentiles). The lightest patient aged between 1-2 years weighed 8.9 kg at Baseline (between the WHO 25th-50th percentiles). In addition, there were two patients aged < 1 year who weighed 9.1 kg and 6.8 kg at Baseline; the latter patient was the lightest patient in the NP25737 study.

To provide additional PK data for the TCZ SC regimen for sJIA patients aged 1-2 years, an additional analysis has been performed for patients in study NP25737. Utilizing the population PK model developed for sJIA patients, the PK characteristics of TCZ in sJIA patients <2 years of age were confirmed to be consistent with those ⩾2 years of age. Individual PK parameters (post-hocs) obtained for each patient in study NP25737 were used to simulate the individual TCZ concentration-time profiles for these 11 patients aged < 2 years for the 162 mg TCZ SC Q2W regimen. Although the data are still relatively limited, the results estimated the range of TCZ exposures that could be expected in sJIA patients aged < 2 years.

For the majority of patients, the steady-state Cmin values were within the range seen in WA28118 for sJIA patients aged ≥1 year. However, 3 patients had higher TCZ exposures; one of these patients was aged <1 year (10.5 months, 6.8 kg), but two patients were aged between 1-2 years (15 months, 10.0 kg; 10.5 months, 9.1 kg).

As expected, Cmax was higher with TCZ IV due to the IV mode of administration.

However, the maximum steady-state Cmin and AUC predicted for TCZ SC for the sJIA patients in NP25737 aged < 2 years (Cmin 253 μg/mL, AUC 3445 μg.h/mL) are higher than seen previously with TCZ SC (WA28118) or TCZ IV (WA18221), and are similar to the exposures in the WA28118 study in <30 kg patients using the SC Q10D regimen (prior to the interim analysis, and dose change to SC Q2W).

2.3.5. Discussion on clinical pharmacology

The main Study WA28118 (JIGSAW 118) was designed to bridge from tocilizumab (TCZ) intravenous (IV) to TCZ subcutaneous (SC) in 1-17-year-old patients with systemic juvenile idiopathic arthritis (sJIA). The study aimed at identifying the SC regimens that achieve comparable PK/PD and safety profiles to the IV regimens established in Study WA18221.

Fifty one (51) patients received 162 mg TCZ in a body weight based manner. Twenty six (26) patients weighing > 30 kg (approximately half of patients) receiving TCZ every week (QW) and patients weighing < 30 kg receiving TCZ every 10 days (Q10D, n=8) or every two weeks (Q2W, n=17; after an interims analysis). Dense and sparse PK samples have been collected, depending on age and body weight of the patients.

There was large variability in the observed TCZ concentration data especially for 3 TCZ naive patients who received the 162 mg Q10D regimen (BW <30 kg). The observed individual pre-dose concentration time courses indicate that the high variability in the Q10D group was triggered by the lightest subject. The CHMP concluded that variability by weight is plausible. However, the predictive performance of the population PK model is limited.

Clinical pharmacokinetics of TCZ was characterized using the population PK approach which includes 140 sJIA patients from Studies WA28118 (n = 51, SC) and WA18221 (n = 89, IV). A two-compartment PK model with parallel linear and Michaelis-Menten eliminations, and first-order absorption was used to describe SC administration and was parameterized in terms of clearance(s) and volume(s) of distribution. The structural model used to describe the PK of TCZ for sJIA is the same as that used to describe the PK of TCZ in pJIA and adult RA patients.

A PK/PD bridging approach was applied for TCZ SC Dose selection, taking a dosing modification after the interim analysis into account. Therefore a population PK analysis based on a pooled data set of 1710 serum samples from 140 paediatric patients with sJIA was conducted.

Overall, structural model parameters were estimated with a good precision (RSE < 12%), except for KM value (RSE = 37%). The same holds for covariate effects which were also precisely estimated (RSE < 14%), except for the BMI-effect on bioavailability Fsc (RSE = 27%) and absorption rate ka (RSE = 87%). Residual variability and variances of the inter-individual random effects were also estimated with a good precision (RSE < 29%), Shrinkage was moderate (< 16%).

Goodness-of-fit plots of the final population PK model show no pronounced deviation from the normal scatter around the identity lines in the observed versus predicted concentration plots. No clear systematic bias could be identified regarding the plots shown above besides the prominent variability. This holds for the IV as well as for the SC mode of administration.

Visual predictive checks (VPC) indicate that the model captures the inter-individual variability in the tocilizumab PK data following IV and SC administration, respectively. Regarding the SC mode of administration, VPC plots show a clear trend of underestimation of concentrations especially following SC Q2W administration. The PK data included from either IV or SC mode of administration were balanced but the diagnostic plots indicate an effect of mode of administration on Clearance. This effect could be due to the small sample size. However, as indicated above, the predictive performance of the population PK model is limited and the observed TCZ concentration levels following SC administration seem to be underestimated. Considering the overall evidence in the present application, the CHMP was of the opinion that this issue would not affect the conclusions; however, the MAH should address the model limitations should it be used in future applications.

The bioavailability estimated by population PK analysis for a typical sJIA patient with a BMI of 18, BSA=1.25 m2, HT=1.432 m, SCRT =43 µmol/L is 94.8% (95% CI: 89.5 – 100%), which is higher compared with that estimated for adult RA patients (79.5%) and similar to that estimated for pJIA patients (96.4%). In addition, body size is indicated to have a clear effect on F with lower F towards the adult value with increasing weight. The absorption rate constant of TCZ following SC administration was estimated by population PK analysis to 0.403 1/day (95% CI: 0.308-0.498 1/day).

The central volume of distribution was estimated for the typical sJIA patient by population PK to 1.87 L (95% CI: 1.75 – 1.99 L) and the peripheral volume of distribution to 2.14 L (95% CI: 1.81 – 2.48 L).

The median effective half-life of TCZ during an inter-dose interval at steady-state varies between 12.2 and 13.5 days for the 162 mg QW regimen in patients weighing > 30 kg. For patients weighing < 30 kg, the median effective half-life of TCZ during an inter-dose interval at steady-state varies between 10.7 and 13.9 days for the 162 mg Q2W regimen. Linear clearance was estimated by population PK analysis to 0.137 L/day for the typical sJIA patient with 95% CI of 0.125 to 0.149 L/day. These parameters are in line with what is expected for TCZ and monoclonal antibodies in general.

Similarly to what has been detected in the pJIA patient group, body size related covariates were shown to have the most pronounced influence on TCZ PK in terms of absorption rate and bioavailability, distribution and elimination. At the CHMP's request, the section 5.2 of the SmPC has been updated to reflect this information (see also discussion below on body weight limit).

Besides, similar to the previous analysis conducted for pJIA patients, serum creatinine was also identified to have an influence on the VM rate constant in sJIA. In addition, gender was identified to have a minor impact on linear CL, VC, VP, and VM. Both effects were not of clinical relevance.

Using the individual Bayesian post hoc parameters estimated using the final population PK model, exposure and concentration-time profiles were simulated for all sJIA patients included in the population PK analysis based on per protocol dosing.

Given that steady state seems to be reached by Week 14, the time point of the interims analysis is acceptable. Assuming a typical half-life of 21 days for a monoclonal antibody, the theoretical accumulation ratio following QW and Q2W dosing regimen can be calculated to 4.8 and 2.7, respectively. Overall, the observed accumulation ratios can be deemed comparable to what is expected.

Comparison of estimated steady-state exposure parameters by regimen and mode of administration indicate an overall good agreement in terms of exposure (especially Cmin). Following SC administration of 162 mg Q2W (BW < 30 kg), median Cmin_ss of 64.15 (16.61 – 135.86) µg/mL is estimated which matches well to Cmin_ss of 65.86 (18.99-135.48) µg/ml that is achieved following 2 mg/kg IV Q2W in the BW < 30 kg group. Median estimated Cmin_ss following 162 mg SC QW and 8 mg/kg IV Q2W are also comparable (72.37 (19.52 – 157.81) µg/mL and 70.73 (5.26 – 126.62), respectively).

The MAH was asked to discuss the discrepancies in the observed PK concentration-time profiles of TCZ following 52 weeks following the Q10D regimen in TCZ naïve sJIA patients compared to the Q2W dosing in the same BW group and also compared to the non-TCZ naïve patients. The observed individual pre-dose concentration time courses indicate that the high variability in the Q10D group could be triggered by the lightest subject.

The observed and individually predicted TCZ Cmin values at steady state were used as a measure of exposure for PD markers and graphical exposure-response analyses regarding efficacy and safety.

Overall, similar levels of efficacy JADAS-71 and CHAQ-DI were observed across the range of exposures in terms of especially PK marker Cmin achieved following TCZ SC administration.

A trend with greater decreases in JADAS-71 was observed for patients treated with the QW regimen (BW > 30 kg) in the low versus high exposure category could be detected, but no clear association could be found between the variability in TCZ exposure and the variability in efficacy, which could partly be attributed to the low sample sizes in each category.

Of note, a direct comparison of exposure-efficacy relationships between TCZ SC and IV in sJIA patients is not possible as JIA ACR30 response and absence of fever were the key efficacy measures in IV Study WA18221 whereas in SC Study WA28118, JADAS-71 was the key efficacy measure under consideration.

A total of 7 patients (13.7%) experienced 9 SAEs during the study. Five of those patients have been assigned to the < 30 kg BW group. Results from the logistic regression analysis showed no relationship between TCZ exposure (Cmin) and SAEs or other marker for safety under consideration.

No correlation between occurrence of serious adverse events (SAEs), any adverse event (AE), any AE Common Terminology Criteria (CTC) Grade 3 or above and AEs of the Infections and Infestations System Organ Class (SOC) and TCZ exposure (Cmin) following SC administration in sJIA could be detected by PK-PD analyses provided. Similarly, no relationship between TCZ exposure (Cmin) and neutropenia AEs or low neutrophil count laboratory abnormalities following TCZ SC in sJIA could be identified.

No other relationship e.g. with Cmax or AUC has been shown. As Cmax is lower following SC administration compared to IV, and AUC is comparable, this is deemed acceptable.

All patients who received TCZ SC in sJIA Study WA28118 & the LTE Study WA29231 were ADA negative. However, due to the very limited number of patients who were ADA positive following TCZ SC and IV administration in, no firm conclusions on the exposure-ADA relationship can be drawn for this indication.

Children aged 1-2 years and weight limit

There were 3 patients in the TCZ SC study, WA28118, who were aged between 1-2 years at baseline. The lightest patient in the study, who weighed 9.2 kg at baseline, was just over 2 years old (25 months).

The data provided by these 3 patients are limited, and based on WHO percentiles, some children below the age of 2 years may have lower BWs and could therefore potentially experience higher TCZ exposures than seen in these 3 patients. To increase confidence in including sJIA patients aged 1-2 years in the TCZ SC label, the MAH has performed additional simulations for this age group, utilizing patient data from TCZ IV study, NP25737.

The population PK model developed for sJIA patients and derived individual PK parameters (post-hocs) obtained for each patient in study NP25737 were used to simulate the individual TCZ concentration-time profiles for 11 patients aged < 2 years (Study NP25737) for the 162 mg TCZ SC Q2W regimen.

Similarly to what has been detected in the pJIA patient group, body weight / body size related covariates were shown to have the most pronounced influence on TCZ PK in terms of distribution, elimination but also absorption and bioavailability, being pivotal for SC way of administration.

As discussed above, the model diagnostics indicated that the model underestimates the observed TCZ concentration levels following SC administration; the predictive performance of the population PK

models is limited, and the between-subject variabilities should be used with caution. As a consequence, the conducted simulations showed a high variability and no confidence bands have been provided. For about half of simulated patients, the steady-state Cmin values were within the range seen in WA28118 for sJIA patients aged >1 year. Of note, 3 patients had higher TCZ exposures. One of these patients was aged <1 year (10.5 months, 6.8 kg), but the other patients were aged between 1-2 years (15 months, 10.5 months) with a body weight around 10 kg (10.0 kg, 9.1 kg). The maximum steady-state Cmin and AUC predicted for TCZ SC for the sJIA patients in NP25737 aged < 2 years (Cmin 253 µg/mL, AUC 3445 µg.h/mL) are higher than seen previously with TCZ SC (WA28118) or TCZ IV (WA18221), and are comparable to the exposures in the WA28118 study in <30 kg patients using the SC Q10D regimen.

In conclusion, additional simulations for age group 1-2 years, utilizing patient data from TCZ IV study, NP25737 provide further data in the 1-2 years age group. TCZ SC regimen will result in PK exposures comparable to those obtained with the approved TCZ IV regimen, when used to treat sJIA patients aged 1-2 years who weigh >10.0 kg. These data support the need of a lower weight cut-off to ensure adequate concentration levels following SC administration. The MAH therefore proposed a lower BW limit of 10.0 kg in sJIA patients aged 1-2 years.

Considering that BW is the main driver for TCZ exposure, the CHMP agreed with the MAH's proposal but also requested that the lower BW limit of 10.0 kg should be set regardless of age, including sJIA patients aged ≥ 2 years. The SmPC has been updated accordingly.

2.3.6. Conclusions on clinical pharmacology

The CHMP considered that the proposed dosing regimen (QW for patients > 30 kg and Q2W for patients < 30 kg) was adequate from a PK perspective. In patients, the TCZ SC regimen will result in PK exposures comparable to those obtained with the approved TCZ IV regimen when used to treat sJIA patients aged 1-2 years.

Body size is the only covariate which has an appreciable impact on the pharmacokinetics of RoActemra including elimination and absorption; hence, body-weight based dosing should be taken into consideration. The lower limit of 10 kg to start the therapy was therefore set as a precautionary step to ensure the TCZ exposure attained in these very young and vulnerable patients remains within the range seen in older children whilst still enabling access to TCZ for the majority of patients. The lower BW limit of 10.0 kg has been set regardless of age i.e. sJIA patients aged 1-2 years and ≥ 2 years. The SmPC has been updated accordingly.

2.4. Clinical efficacy

2.4.1. Main study

WA28118 – A Phase Ib, Open-Label, Multicenter Study to Investigate the Pharmacokinetics, Pharmacodynamics, and Safety of Tocilizumab Following Subcutaneous Administration to Patients With Systemic Juvenile Idiopathic.

Methods

Study WA28118 (otherwise known as JIGSAW 118) was a Phase Ib, 52-week, open label, multicentre, PK/PD and safety study in paediatric patients with sJIA, aged 1 to 17 years old (12 to 17 years old for patients in Russia). The study aimed to identify the SC regimens that achieve comparable PK/PD and safety profiles to the approved IV regimens established in Study WA18221. The TCZ SC treatment was administered using a PFS + NSD.

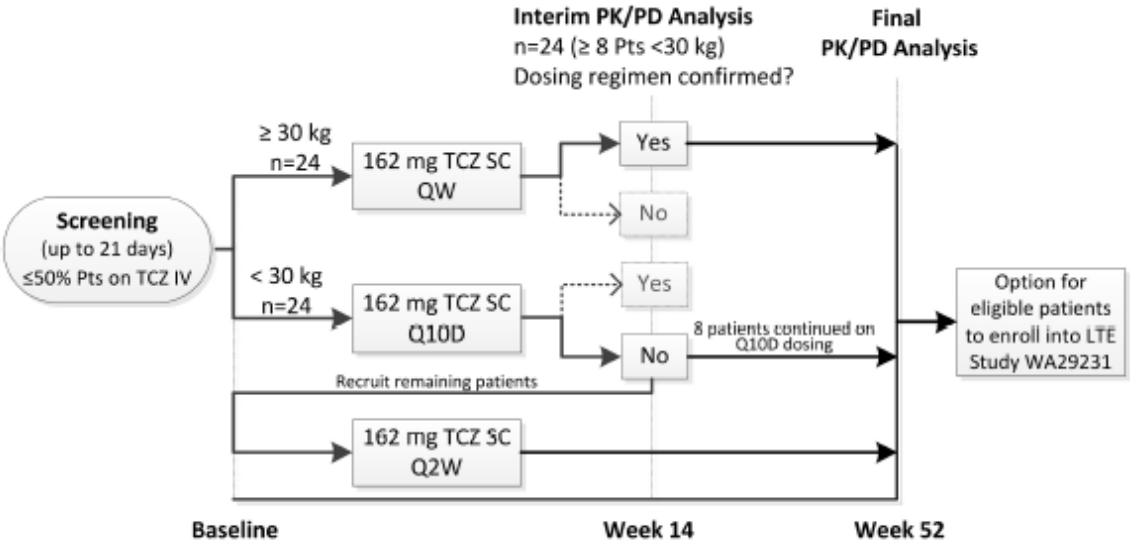


Figure 10 Overview of TCZ SC WA28118 Study Design

Objectives in study WA28118 (Jigsaw 118) were to characterize the pharmacokinetics of subcutaneous (SC) tocilizumab (TCZ), to evaluate the pharmacodynamics of SC TCZ, and to evaluate the safety of SC TCZ in patients with pcJIA. The efficacy of SC TCZ in patients with pcJIA was an exploratory objective.

Following review of the data from the planned interim analysis of the first 28 patients (8 patients <30kg and 20 patients ≥ 30kg); who completed Week 14 of the study the dosing regimen for patients weighing < 30 kg was changed from Q10D to Q2W. The QW dosing regimen for the $\geq$ 30 kg BW group remained unchanged.

Study participants

Children aged 1 year (12 years for patients in Russia) up to and including 17 years with a diagnosis of sJIA who had an inadequate response to NSAIDs and corticosteroids, including patients with well-controlled disease receiving treatment with TCZ IV (including patients who participated in Study WA18221; no more than 50% should have switched from commercially available TCZ IV to TCZ SC at baseline) and TCZ naive patients with active disease were eligible for inclusion in the study.

Patient who received previous treatment with biologic agents other than TCZ (e.g. etanercept, anakinra, abatacept, infliximab or adalimumab, canakinumab or rilonacept), these must have been discontinued according to specified timelines prior to the baseline visit.

Patients who received TCZ IV at study initiation and with well-controlled disease could enter the study without a period of TCZ discontinuation and received their first dose of TCZ SC on the date that their next IV infusion would have been due.

Patients with disease that was well controlled by any therapeutic agent other than TCZ were not considered for inclusion in this study.

Treatments

TCZ was provided in a pre-filled syringe with a needle safety device (PFS + NSD, 162 mg TCZ/0.9 mL solution):

- Patients weighing < 30 kg enrolled prior to interim analysis: TCZ SC Q10D (Q2W)
- Patients weighing < 30 kg enrolled after interim analysis: TCZ SC Q2W
- Patients weighing $\geq$ 30 kg entire study: TCZ SC QW

Concurrent treatment with DMARDs (including methotrexate [MTX]), NSAIDs, and oral corticosteroids was permitted at the discretion of the investigator.

Immunosuppressants such as cyclosporine and cyclophosphamide, and biologic agents other than TCZ were prohibited during the study.

Objectives

- Pharmacokinetic (PK) Objective: to characterize the pharmacokinetics of TCZ SC in patients with sJIA
- Pharmacodynamic (PD) Objective: to evaluate the pharmacodynamics of TCZ SC in patients with sJIA
- Safety Objective: evaluate the safety of TCZ SC in patients with sJIA
- Exploratory Objective: to describe the efficacy of TCZ SC in patients with sJIA

Outcomes/endpoints

Pharmacokinetics

- Serum TCZ concentration and population PK model-predicted PK exposures (AUC, maximum concentration [Cmax], and Cmin) for the for the initial QW and Q10D dosing regimens at

steady state, and the Q2W dosing regimen at steady state in the < 30 kg patients (after the interims analysis)

Pharmacodynamics

- Serum IL-6 and sIL-6R levels, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)
- The incidence of anti-TCZ antibodies

Safety

- The incidence and severity of AEs (including local injection-site reactions) and SAEs
- The incidence and severity of adverse events of special interest
- The incidence and severity of clinical laboratory abnormalities

Efficacy (exploratory)

- Juvenile Arthritis Disease Activity Score (JADAS)-71
- Inactive disease and clinical remission
- Childhood Health Assessment Questionnaire (CHAQ)

Previously in the TCZ IV Study WA18221, JIA ACR response was used as the primary efficacy endpoint measure. In the current study JADAS-71 was used instead of the JIA ACR 30/50/70/90 responses because it has the advantage of not relying on a percentage change from baseline (CFB), while still providing a robust efficacy measure, which includes many of the same or analogous variables as the JIA ACR response measurement. A change from baseline based response measure would not be appropriate to evaluate maintenance of response from patients who switched from TCZ IV to TCZ SC in Study WA28118. For comparison purposes, JADAS-71 was calculated post hoc for the TCZ IV Study WA18221 as all of the JADAS-71 component data were collected.

Sample size

Based on the methodology proposed in Wang et al. (2012) for determining sample size for paediatric PK studies, an initial sample size of approximately 48 patients was to allow targeting a probability (power) of at least 80% to have the 95% confidence interval (CI) within 60% and 140% of the population mean estimates for the PK parameters in the age group to be studied. The population mean estimates for the PK parameters were obtained from a population PK model developed using data from Study WA18221. The results were obtained from 1000 simulations of trials with 51 patients with PK samples under the planned sampling schema based on the two compartment model with a combined linear and nonlinear elimination that was developed for patients with sJIA.

A sample size of approximately 48 patients completing all study treatments and assessments, up to and including Week 14 (n = 24 per group), was deemed adequate to meet the above criterion and the PK/PD objectives of this study.

In the event of the planned interim analysis of the PK data was to suggest that an alternative dosing regimen(s) was to be studied, the total sample size may have been increased to a maximum of 72 patients (i.e., up to another 48 patients in case both doses had to be changed) to ensure that there were enough data to evaluate the pharmacokinetics, pharmacodynamics, and safety of the treatment at the chosen dose.

A sample size of 48 patients completing the study was to ensure a 95% probability of observing at least one AE for which the underlying incidence of that event is ≥ 6.1%. However, this was not the primary goal of the study.

Randomisation

WA28118 was a single-arm study. Patients were assigned to one of two dose groups based on body weight.

Blinding (masking)

Patients, parents/guardians, investigators, and the MAH were not blinded to treatment assignment, as this was a single-arm, open-label study.

Statistical methods

All statistical analyses for the efficacy endpoints are descriptive in nature.

Three analysis populations were foreseen: a PK/PD population (per-protocol analysis, including all patients enrolled and adherent to the protocol), a safety population (as-treated, patients who received ≥1 dose of treatment and who had at ≥ 1 post-dose safety assessment) and an ITT population (enrolled who received ≥1 dose of treatment).

JADAS-71, inactive disease, and clinical remission rates was planned to be summarized over time within treatment groups to assess the efficacy of SC TCZ in sJIA. Absolute and change from baseline values for JADAS-71 data by visit were to be summarized by TCZ status (naïve or pre-treated), BW category (< 30 kg, ≥ 30 kg), and for "All TCZ."

For the JADAS-71, inactive disease, and clinical remission, last observation carried forward (LOCF) of the latest post baseline value was to be applied to core set components. At a visit, patients who were missing all core set components were to be excluded.

Interim analysis

An interim population PK analysis was to be conducted during this study based on PK data from approximately the first 24 patients that have completed 14 weeks of treatment. In addition, all available PD, safety, and efficacy data was to be reviewed during interim analysis. At least 8 patients weighing < 30 kg were to be included in this analysis. The total number of patients switching from IV TCZ were not to account for more than 50% of the total subject number at both interim and final PK analysis stages.

Patients whose data was to be used in the interim analysis would have completed the PK assessment phase (to Week 14/Day 100) to confirm that the proposed SC dosing regimen is generating the expected Cmin distribution. The population PK model was to be developed by pooling the SC PK data with the IV data from Study WA18221 to properly characterize the PK properties of the SC formulation. Simulations were to be conducted to confirm that the selected 162-mg Q10D regimen for < 30 kg BW regimen and the 162-mg QW for the ≥ 30 kg BW regimen are able to achieve at least a similar distribution of steady-state Cmin compared with IV TCZ.

In the scenario in which major discrepancies were shown between the two distributions, simulations were to be conducted using the population PK model to identify alternative dosing regimens that would

generate more comparable distributions between IV and SC. If different dosing regimens were identified in the interim stage, patients already enrolled will be switched to the new regimen at the next appropriate visit.

Further guidance regarding dose regimen switching was to be provided in a separate guidance document. Owing to the possibility of dose regimen modification, the total sample size may have been increase to a maximum of 72 patients, see paragraph on sample size above.

Results

Participant flow

Of 57 patients screened, a total of 51 patients were enrolled into this study and received TCZ.

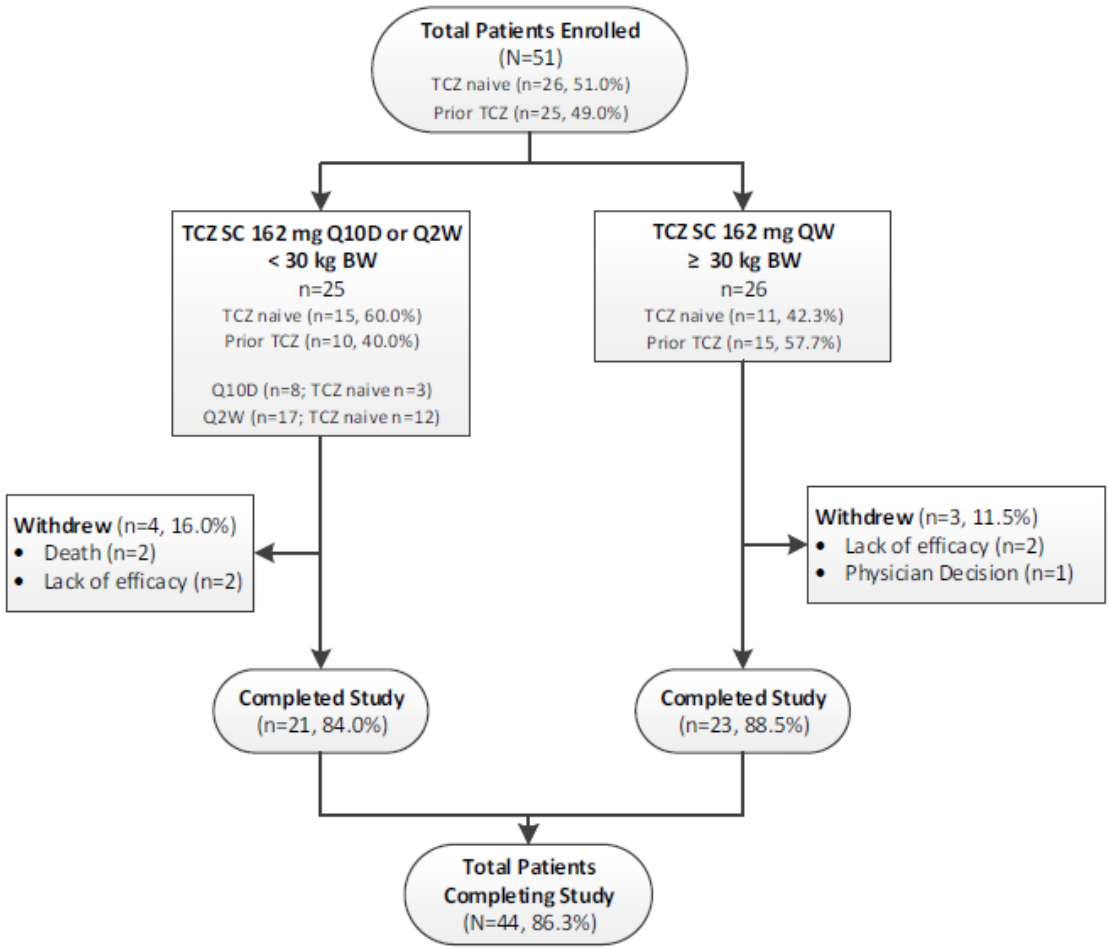


Figure 11 Patient disposition

The most common reasons for screening failure were 'met exclusion criteria'.

Patients received open-label TCZ SC treatment based on BW at baseline, with 25 patients weighing < 30 kg receiving 162 mg of TCZ Q10D (8 patients enrolled prior to interim analysis) or Q2W (17 patients enrolled after interim analysis) and 26 patients weighing ≥ 30 kg receiving 162 mg of TCZ QW. The 8 patients weighing < 30 kg on Q10D dosing remained on this dosing regimen throughout the

entire study. One patient, initially weighing < 30 kg and on Q10D dosing, switched to QW dosing from Day 218 onward following a body weight increase to ≥ 30 kg.

Conduct of the study

There were five study protocol amendments to the original protocol.

Protocol Amendment, Version 2 (19 March 2013)

- Replacement of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) as a patient-reported outcome (PRO) with the CHAQ functional ability instrument (for legal reasons).
- Switch to the 100 mm VAS scale for the purposes of consistency (as the CHAQ uses 100 mm VAS scales as opposed to the 21-circle scale used in JAMAR)
- Update of the immunogenicity testing requirements for patients who withdrew due to hypersensitivity or anaphylaxis
- Clarification of dose interval for patients whose BW increased or decreased above or below the30 kg threshold

Protocol Amendment, Version 3 (8 May 2013, Russia)

- Revision of the inclusion criteria for the age range of patients to 12−17 years of age
- Protocol Amendment, Version 4 (5 August 2013)
- To limit the number of patients switching from TCZ IV to TCZ SC to no more than 50% of the total number of subjects and to include the request to collect information on the prior four IV infusions for patients switching from TCZ IV to TCZ SC.

Protocol Amendment, Version 5 (2 March 2015)

- Change of the dosing regimen for patients weighing < 30 kg from Q10D to Q2W following the review of the planned interim analysis.
- This change was applicable to all newly enrolled patients weighing < 30 kg as well as to patients weighing < 30 kg already enrolled in the study and receiving Q10D as per the initial dosing regimen.
- *Of note this protocol amendment was finalised but not submitted to the Health Authorities or study sites as further updates were identified prior to submission.*

Protocol Amendment, Version 6 (23 June 2015)

- Protocol amendment Version 6 included the change in dosing regimen for patients as described in Version 5 and was submitted the Health Authorities and study sites. Additional minor changes were included in this protocol amendment.
- It was planned that patients weighing < 30 kg enrolled prior to the interim analysis would switch from a Q10D to a Q2W dosing regimen; however, these patients had completed the study by the time this protocol amendment was approved and implemented.

Baseline data

The majority of the patients were females (56.9%), white (80.4%) and of non-Hispanic or Latino ethnicity (76.5%). The two BW groups differed in median age (5 years vs. 14 years), median height (104.5 cm vs. 154.8 cm), and median weight (19.6 kg vs. 51.7 kg), which is as expected for these BW dosing groups. Three patients were under the age of 2 years at baseline (17, 19 and 22 month)

The proportion of patients on background oral corticosteroids at baseline was higher in the < 30 kg BW group (< 30 kg: 80.0% vs. ≥ 30 kg: 46.2%). Whereas previous use of a non-biologic DMARD (including MTX; < 30 kg: 56.0% vs. ≥ 30 kg: 92.3%) and biologic DMARD (< 30 kg: 56.0% vs. ≥ 30 kg: 88.5%) was lower in the < 30 kg BW group, background methotrexate use was similar in both BW groups (< 30 kg: 52.0% vs. ≥30 kg: 53.8%).

TCZ naive patients in the < 30 kg BW group had higher median JADAS-71 results (< 30 kg: 15.10 vs. ≥ 30 kg: 13.20) including each JADAS-71 component, higher mean CHAQ-DI scores (1.28 vs. 0.78, respectively), as well as a higher mean number of active joints (11.6 vs. 6.6, respectively), mean ESR (38.1 mm/hr vs. 31.8 mm/hr, respectively) and mean CRP levels (41.1 mg/L vs. 25.4 mg/L, respectively) compared with TCZ naïve patients in the ≥ 30 kg BW group. As expected, patients in both BW groups who were naive to TCZ had higher median JADAS-71 and mean CHAQ-DI scores at baseline, and a higher number of active joints compared with those patients with prior TCZ experience.

Table 11 Key demographics and disease characteristics at baseline for WA28118

	TCZ SC (WA28118)			
	162 mg SC Q10D or Q2W (< 30 kg) N = 25		162 mg SC QW (≥ 30 kg) N = 26	
	TCZ Naive n = 15	Prior TCZ n = 10	TCZ Naive n = 11	Prior TCZ n = 15
Age (years), mean (SD) Min – Max	5.2 (3.0) 2 – 13	4.9 (3.6) 1[a] – 10	13.1 (3.2) 8 – 17	13.5 (3.2) 6 – 17
Males, n (%)	8 (53.3%)	4 (40.0%)	5 (45.5%)	5 (33.3%)
Females, n (%)	7 (46.7%)	6 (60.0%)	6 (54.5%)	10 (66.7%)
Weight (kg), mean (SD) Min – Max	19.1 (5.4) 9.2 – 27.0	18.1 (6.4) 10.3 – 27.2	52.2 (14.3) 30.0 – 73.2	51.3 (12.8) 33.3 – 72.9
Prior non-biologic DMARD use, n (%)	7 (46.7%)	7 (70.0%)	9 (81.8%)	15 (100.0%)
Prior biologic DMARD use, n (%)	4 (26.7%)	10 (100.0%)	8 (72.7%)	15 (100.0%)
Background oral CS use, n (%)	14 (93.3%)	6 (60.0%)	8 (72.7%)	4 (26.7%)
Background MTX use, n (%)	8 (53.3%)	5 (50.0%)	5 (45.5%)	9 (60.0%)
ESR (mm/hr), mean (SD)	38.1 (29.7)	3.1 (2.1)	31.8 (27.9)	4.2 (4.3)
CRP (mg/dL), mean (SD)	41.1 (50.5)	0.5 (0.5)	25.4 (39.2)	0.2 (0.1)
JADAS-71 (0-101), median (Min – Max)	15.1 (7.7 – 53.1)	2.5 (0.0 – 10.5)	13.2 (1.9 – 46.9)	1.0 (0.0 – 17.8)
CHAQ-DI Score (0-3), mean (SD)	1.28 (0.93)	0.28 (0.42)	0.78 (1.00)	0.45 (0.77)

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.

CHAQ-DI = Childhood Health Assessment Questionnaire Disability Index; CS = corticosteroid; DMARD = Disease-Modifying Anti-Rheumatic Drug; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; JADAS = Juvenile Arthritis Disease Activity Score; MTX = methotrexate; SD = standard deviation.

[a] 3 patients < 2 years old (17 months, 19 months, and 22 months) at baseline were recruited into the study.

Numbers analysed

All 51 patients enrolled received at least one dose of treatment (i.e., met the ITT population definition) and had at least one post-dose safety assessment qualifying them for the safety population.

No patient had significantly violated the inclusion or exclusion criteria, deviated significantly from the protocol, or had unavailable or incomplete data and, therefore, the PK/PD population is also equivalent to the safety population.

One patient weighing ≥ 30 kg took the growth hormone somatropin during the study, and another patient weighing ≥ 30 kg had a history of somatropin use. However, no patient was excluded from growth analyses, for which the safety population was used (see below).

Table 12 Summary of analysis populations

	TCZ SC 162 mg Q10D or Q2W (< 30 kg) (N=25)	TCZ SC 162 mg QW (>= 30 kg) (N=26)	All TCZ (N=51)
Safety Population	25	26	51
Total Exclusions	0	0	0
ITT Population	25	26	51
Total Exclusions	0	0	0
PK/PD Population	25	26	51
Total Exclusions	0	0	0

Protocol deviations

A total of 6 patients (2 in the < 30 kg BW group and 4 in the > 30 kg BW group) had a total of 7 major protocol deviations, none of which were considered significant enough to exclude them from the PK/PD population. One of these patients in the > 30 kg BW group did not complete the study. Three protocol deviations were in the 'medication' category (administration of prohibited vaccine [2] and administration of incorrectly stored drug), two in the 'exclusion criteria' category (missing laboratory values prior to randomization and missing bilirubin value at screening), and another two in the 'procedural' category (PK sample not taken at single time point and no re-consent of updated version of the ICF).

Outcomes and estimation

The efficacy results for TCZ SC Study WA28118 are exploratory in nature as the study was not controlled and the number of patients who were TCZ naive in WA28118, for whom the efficacy evaluation is most informative, was low (n = 26). JADAS-71 was used as the key efficacy endpoint measure in the study.

JADS 71

JADAS-71 scores generally improved (decreased) over the course of the study for patients initiating TCZ treatment (TCZ naive patients), and were maintained or improved further for patients who switched from TCZ IV to TCZ SC (prior TCZ patients), irrespective of BW group (i.e., < 30 kg or > 30 kg).

In TCZ naive patients, the median JADAS-71 decreased from baseline to Week 52 by 13.90 for patients in the < 30 kg BW group and 12.40 for patients in the > 30 kg BW group. In these TCZ naive patients, the median JADAS-71 value reduced to the level of inactive disease (< 1.0) by Week 26 in both BW groups, and generally remained at this level for rest of the study

Table 13 JADAS-71 results in TCZ naive SC (WA28118) patients

	TCZ Naive SC (WA28118)		
	162 mg Q10D or Q2W (<30 kg)	162 mg QW (≥30 kg)	All TCZ Naive
JADAS-71	n = 15	n = 11	n = 26
Baseline	n = 15	n = 11	n = 26
Median	15.10	13.20	14.85
(min – max)	(7.7 – 53.1)	(1.9 – 46.9)	(1.9 – 53.1)
Mean (SD)	23.60 (15.59)	15.90 (12.43)	20.34 (14.59)
Week 10	n = 14	n = 11	n = 25
Median	3.25	2.00	3.20
(min – max)	(0.4 – 36.3)	(0.0 – 13.9)	(0.0 – 36.3)
Mean (SD)	7.86 (11.78)	4.34 (4.65)	6.31 (9.35)
Week 30	n = 14	n = 11	n = 25
Median	1.10	1.30	1.30
(min – max)	(0.0 – 12.0)	(0.1 – 18.4)	(0.0 – 18.4)
Mean (SD)	1.94 (3.12)	4.07 (5.59)	2.88 (4.41)
Week 52	n = 12	n = 11	n = 23
Median	0.30	0.20	0.20
(min – max)	(0.0 – 6.0)	(0.0 – 5.7)	(0.0 – 6.0)
Mean (SD)	1.31 (1.83)	1.25 (1.73)	1.28 (1.74)

WA28118: LOCF applied to missing core components at visits. WA18221 LTE: Each visit includes patients with a non-missing assessment at the time point.
[a] The 'All TCZ' group presented for WA18221 has an n = 112 because it includes patients who switched from one of the two TCZ doses during the study; these 'switcher' groups 'TCZ 8 mg/kg to TCZ 12 mg/kg' n = 1 and 'TCZ 12 mg/kg to TCZ 8 mg/kg' n = 9 are not shown.

Prior TCZ patients had lower baseline JADAS-71 values compared with TCZ naive patients in both BW groups, and the low values were maintained below the level of minimal disease activity. Thus, patients who entered the study previously receiving TCZ IV treatment were able to maintain disease control, as reflected by JADAS-71. Prior TCZ patients in the < 30 kg BW group had median JADAS-71 values below the level of inactive disease from Week 18 through Week 52 (baseline score 2.45), while for the > 30 kg BW group, the median JADAS-71 values were below the level of inactive disease from Week 4 through Week 52 (baseline score 1.00).

The median JADAS-71 results of TCZ naive patients were similar to those from patients with prior TCZ experience from Week 22 through Week 52.

JADAS-71 Components

- **Physician Global Assessment VAS**

Physician global assessment of disease activity VAS was recorded on a scale of 0 - 100 mm, 0 mm for no arthritis symptoms and 100 mm for maximum arthritis symptoms.

In TCZ naive patients, the mean VAS profiles of the two BW groups were similar. In TCZ naive patients weighing < 30 kg, the mean VAS decreased from 46.3 mm at baseline to 12.7 mm at Week 6 and remained below 10.0 mm from Week 18 through Week 52. In TCZ naive patients weighing < 30 kg, the mean VAS decreased from 39.7 mm at baseline to 15.3 mm at Week 6 and remained at or below 10.0 mm from Week 8 through Week 52.

Prior TCZ patients in both BW groups had lower baseline physician global assessment VAS values compared with TCZ naive patients. The already low VAS scores for prior TCZ patients at baseline (< 30 kg: 8.8 mm; > 30 kg: 5.7 mm) were generally maintained throughout the study and improved for both BW groups by Week 52 (< 30 kg: 1.3 mm; > 30 kg: 0.9 mm).

- **Number of Active Joints**

An overall improvement (decrease) in actively diseased joints was observed in TCZ naive patients in both BW groups, and the already low number of active joints at baseline in the prior TCZ patients was generally maintained in both BW groups to the end of the study.

In TCZ naive patients weighing < 30 kg, the mean number of active joints decreased from 11.6 at baseline to 2.8 at Week 6 and further decreased to < 1 from Week 30 through Week 52 (0.2 mean active joints). In TCZ naive patients weighing > 30 kg, the mean number of active joints decreased from 6.6 at baseline to 3.0 at Week 6 and further decreased to < 1 from Week 46 through Week 52 (0.5 mean active joints).

Patients with prior TCZ experience had low mean active joint numbers at baseline (< 30 kg: 1.3; > 30 kg: 1.2) and remained low throughout the study (Week 52: < 30 kg: 0.1; > 30 kg: 0.0).

At Week 52, 52.2% (12/23) of TCZ naive patients and 40.0% (8/20) of prior TCZ patients had no active joints (i.e. a number of 0).

- **Erythrocyte Sedimentation Rate (ESR)**

In TCZ naive patients weighing < 30 kg, the mean ESR decreased from 38.10 mm/hr at baseline to 7.64 mm/hr at Week 4 and further decreased to 4.10 mm/hr at Week 6, and remained low through Week 52 (1.82 mm/hr). In TCZ naive patients weighing > 30 kg, the mean ESR decreased from 31.82 mm/hr at baseline to 5.36 mm/hr at Week 4 and was maintained at this rate through Week 52 (4.55 mm/hr).

Patients with prior TCZ experience (both BW groups) had low mean ESRs at baseline of 3.10 mm/hr (< 30 kg) and 4.20 mm/hr (> 30 kg), which were maintained at similarly low levels through Week 52 (< 30 kg: 2.50 mm/hr; > 30 kg: 2.83 mm/hr).

- **C-Reactive Protein (CRP)**

For TCZ naive patients weighing < 30 kg, the mean CRP decreased from 41.08 mg/mL at baseline to 0.26 mg/mL at Week 12 and remained below 3 mg/mL through Week 52. Post-baseline mean CRP levels above the normal range (> 3 mg/mL) were present at Week 2 (10.12 mg/mL), Week 4 (12.13 mg/mL) and marginally at Week 6 (3.74) and Week 10 (3.10 mg/mL). The elevated CRP levels at Weeks 2, 4 and 6 were driven by a single patient (initially on Q2W dosing) with values of 139 mg/mL, 150 mg/mL, and 27.7 mg/mL, respectively. This patient had an AE of tooth abscess (Grade 1) reported at Week 6. Given that this patient had an improvement in JADAS-71 at Week 6 (a decrease of 19.2 from baseline), the CRP spike was not considered to be related to a sudden increase in sJIA disease

activity. The patient's maximum CRP level from Week 10 through Week 34 (last visit prior to death, see section 5) was 1.06 mg/mL.

For TCZ naive patients weighing > 30 kg, the mean CRP decreased from 25.42 mg/mL at baseline to 1.38 mg/mL at Week 1 and remained within the normal range (below 3 mg/mL) through Week 52.

- **Pain VAS**

Pain VAS was assessed on a scale of 0 - 100 mm, 0 for no pain and 100 mm for very extreme pain

Table 14 Pain VAS results in TCZ naive SC (WA28118) patients

	TCZ Naive SC (WA28118)		
Pain VAS (mm)	162 mg Q10D or Q2W (< 30 kg) n = 15	162 mg QW (≥ 30 kg) n = 11	All TCZ Naive n = 26
Baseline	15	11	26
Median	57.0	32.0	50.0
(min – max)	(5 – 91)	(1 – 84)	(1 – 91)
Mean (SD)	52.5 (30.1)	32.0 (30.5)	43.8 (31.4)
Week 10	13	10	23
Median	16.0	11.0	14.0
(min – max)	(0 – 50)	(0 – 39)	(0 – 50)
Mean (SD)	19.2 (19.4)	15.8 (16.1)	17.7 (17.7)
Week 30	14	11	25
Median	2.0	11.0	4.0
(min – max)	(0 – 37)	(0 – 80)	(0 – 80)
Mean (SD)	8.6 (12.2)	15.0 (22.8)	11.4 (17.5)
Week 52	10	11	21
Median	0.0	2.0	1.0
(min – max)	(0 – 27)	(0 – 15)	(0 – 27)
Mean (SD)	3.6 (8.5)	4.5 (5.7)	4.0 (7.0)

IV = intravenous; Q10D = every 10 days; Q2W = every 2 weeks; QW = every week; SC = subcutaneous; TCZ = tocilizumab.

[a] The 'All TCZ' group presented for WA18221 has an n = 112 because it includes patients who switched from one of the two TCZ doses during the study; these 'switcher' groups 'TCZ 8 mg/kg to TCZ 12 mg/kg' n = 1 and 'TCZ 12 mg/kg to TCZ 8 mg/kg' n = 9 are not shown.

An overall improvement (decrease) in mean pain VAS from baseline to Week 52 was observed in TCZ naive patients (both BW groups). In prior TCZ patients (both BW groups), the already low mean pain VAS at baseline was generally maintained throughout the study, and slightly improved by Week 52.

For TCZ naive patients weighing < 30 kg, the mean pain VAS decreased from 52.5 mm at baseline to 19.2 mm at Week 10, and further decreased below 10 mm from Week 22 through Week 52. TCZ naive patients weighing ≥ 30 kg had a lower baseline mean pain VAS of 32.0 mm that decreased to 10.2 mm at Week 4, and thereafter ranged between 4.5 to 15.8 mm through Week 52.

Patients with prior TCZ use had lower mean pain VAS at baseline (< 30 kg: 11.8 mm; ≥ 30 kg: 15.5 mm) compared with TCZ naive patients. The already low mean pain VAS at baseline was generally maintained throughout the study and slightly improved by Week 52 for both BW groups.

Inactive disease

Table 15 Proportion of patients with inactive disease at visits by BW group and prior TCZ use

	All TCZ (N = 51)			
	< 30 kg (n=25)		≥ 30 kg (n=26)	
Visit	TCZ Naive n=15	Prior TCZ n=10	TCZ Naive n=11	Prior TCZ n=15
Baseline	0/15	5/10 (50%)	0/11	8/15 (53.3%)
Week 10/12[a]	3/10 (30.0%)	4/5 (80.0%)	1/11 (9.1%)	10/13 (76.9%)
Week 26	12/14 (85.7%)	7/8 (87.5%)	6/11 (54.5%)	10/12 (83.3%)
Week 38	12/13 (92.3%)	6/8 (75.0%)	6/11 (54.5%)	11/12 (91.7%)
Week 52	10/13 (76.9%)	7/8 (87.5%)	6/11 (54.5%)	12/12 (100.0%)

[a] Week 10 for patients in the < 30 kg BW group and Week 12 for patients in the ≥ 30 kg BW group.

An increasing proportion of patients had inactive disease over the course of the study, irrespective of TCZ status or BW group. By Week 52, 66.7% (16/24) of TCZ naive patients and 95.0% (19/20) of prior TCZ patients had inactive disease.

Clinical remission

Table 16 Proportion of patients in clinical remission at visits by BW group and prior TCZ use

	All TCZ (N = 51)			
	< 30 kg (n=25)		≥ 30 kg (n=26)	
Visit	TCZ Naive n=15	Prior TCZ n=10	TCZ Naive n=11	Prior TCZ n=15
Week 26	0/14	5/8 (62.5%)	0/11	7/12 (58.3%)
Week 38	3/13 (23.1%)	5/8 (62.5%)	1/11 (9.1%)	8/12 (66.7%)
Week 52	8/13 (61.5%)	6/8 (75.0%)	4/11 (36.4%)	9/12 (75.0%)

Childhood Health Assessment Questionnaire – Disability Index (CHAQ-DI)

Table 17 Proportion of patients with a minimal clinically important improvement from baseline in CHAQ-DI score at visits by BW and TCZ status

	All TCZ (N = 51)			
	< 30 kg (n=25)		≥ 30 kg (n=26)	
Visit	TCZ Naive n=15	Prior TCZ n=10	TCZ Naive n=11	Prior TCZ n=15
Week 10	9/13 (69.2%)	1/9 (11.1%)	4/10 (40.0%)	2/13 (15.4%)
Week 18	11/14 (78.6%)	1/9 (11.1%)	5/11 (45.5%)	2/12 (16.7%)
Week 26	11/14 (78.6%)	2/8 (25.0%)	5/11 (45.5%)	2/12 (16.7%)
Week 38	10/13 (76.9%)	1/8 (12.5%)	6/11 (54.5%)	2/12 (16.7%)
Week 46	11/13 (84.6%)	3/8 (37.5%)	6/11 (54.5%)	3/12 (25.0%)
Week 52	9/10 (90.0%)	3/8 (37.5%)	6/11 (54.5%)	3/12 (25.0%)

CHAQ-DI = Childhood Health Assessment Questionnaire - Disability Index.
n represents the total number of patients with non-missing CHAQ-DI assessment at the time point.
Responders are patients who had at least a 0.13 improvement in the CHAQ-DI score from Baseline to the visit.
Each visit includes patients with a non-missing assessment at the time point.
Percentages are calculated based on n. Patients who previously withdrew were excluded.
Patients without a Baseline assessment were excluded.
Weeks 4 and 8 are not presented in this summary table because these time points include data from patients in the < 30 kg BW group on Q10D dosing only and not those on Q2W dosing. Week 6 includes only data for patients on Q2W dosing within the < 30 kg BW group.

In TCZ naive patients, improvements in mean CHAQ-DI scores from baseline to Week 52 were observed in both BW groups. In the prior TCZ patients, improvements in mean CHAQ-DI scores from baseline to Week 52 were observed in the ≥ 30 kg BW group, while for the < 30 kg BW group, the mean CHAQ-DI scores were maintained around the already low baseline value during the study.

In TCZ naive patients weighing < 30 kg, the mean ± standard deviation (SD) CHAQ-DI score decreased from the baseline value of 1.28 ± 0.93 to 0.57 ± 0.68 at Week 6 and continued to decrease to 0.01 ± 0.04 (%CFB at Week 52: -99.2%) at Week 52. In TCZ naive patients weighing ≥ 30 kg, the baseline mean CHAQ-DI score of 0.78 ± 1.00 decreased to 0.36 ± 0.77 at Week 6 and generally remained around this level through Week 42, and then continued to decrease ending at 0.25 ± 0.56 at Week 52 (%CFB at Week 52: - 78.2%). From Week 30 through Week 52, the mean CHAQ-DI scores were improved (lower) in TCZ naive patients weighing ≤ 30 kg compared with TCZ naïve patients weighing > 30 kg. It should be noted that one TCZ naive patient in the ≥ 30 kg BW group had consistently high CHAQ-DI scores (≥ 2) throughout the study.

In prior TCZ patients weighing < 30 kg, the low mean baseline CHAQ-DI score of 0.28 ± 0.42 was generally maintained throughout the study, ending with a mean CHAQ-DI score of 0.03 ± 0.06 (Week 52; %CFB: -78.2). In prior TCZ patients weighing ≥ 30 kg, the mean CHAQ-DI score at baseline of 0.45 ± 0.77 generally improved over the course of the study ending at 0.00 ± 0.00 at Week 52 (%CFB at Week 52: - 100%).

Growth

Tanner stage was not collected in this study. Therefore, the ≥ 30 kg BW group includes patients who had reached puberty and attained their final adult height, creating bias within this group.

One patient in the ≥ 30 kg BW group had 10 years of somatropin use that stopped 4 years prior to the study. One patient in the ≥ 30 kg BW group started somatropin therapy approximately 2.3 years prior to the study and was on stable dosing throughout the study. These two patients were included in the growth analyses.

Table 18 Mean Height Standard Deviation Scores at baseline, Month 6 and Year 1 (Study WA28118)

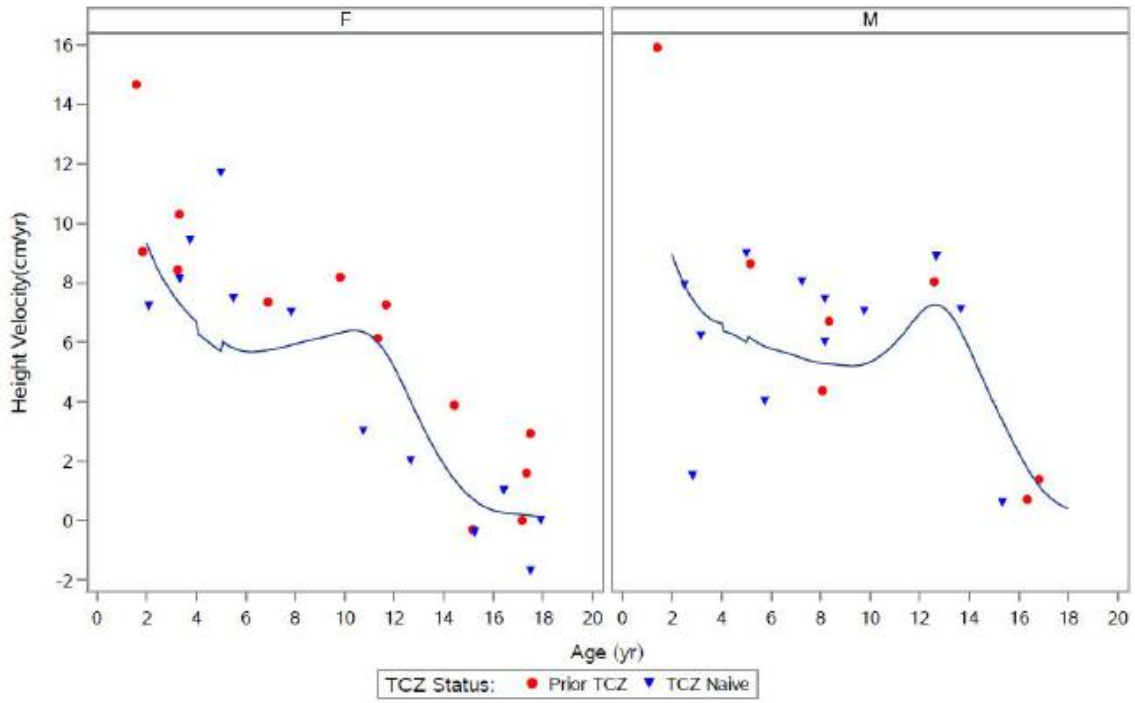
	All TCZ (N = 51)			
	TCZ Naive (n=26)		Prior TCZ (n=25)	
Visit	< 30 kg n=15	≥ 30 kg n=11	< 30 kg n=10	≥ 30 kg n=15
Baseline	–1.22 (15)	–0.26 (11)	–0.78 (10)	0.03 (15)
Month 6	–1.16 (14)	–0.31 (11)	–0.01 (9)	0.16 (12)
Year 1	–0.77 (13)	–0.32 (11)	0.27 (8)	0.22 (12)

Values show mean height SDS (n).

At baseline, the mean height SDS of TCZ naive patients in the < 30 kg BW group was below the normal reference range, and increased at Month 6 and Year 1 in this group, indicating improvement from baseline towards the normal reference height. Mean baseline height SDSs for the other three subgroups (TCZ naive in the ≥ 30 kg BW group and prior TCZ patients in both BW groups) were closer to the normal reference height at baseline, and showed increases or remained stable over the 12 month period, indicating minor improvement or normal growth. Overall, individual patient's height SDSs remained mostly stable or improved over the course of the study

Height velocity

Overall, the distribution of height velocities observed was consistent with expected height velocities for female and male patients during a year based on WHO norms, which are shown as the solid curves. This is further displayed in the plot of one-year height velocity against WHO expected 1 year height velocity. This confirms that patients displayed a normal pattern of growth during the study period. Over the course of the study, individual one-year height velocities exceeded WHO expectations for 15/29 (51.7%) females and 13/22 (59.1%) males.



Height velocity is calculated as ((height at timepoint - height at baseline) / (time between observations in days)) * 365.25
Solid line shows WHO expected height velocity at each age.
Program: /opt/BIOSTAT/prod/cn11935d/i28118b/g_grwth_hv_age.sas
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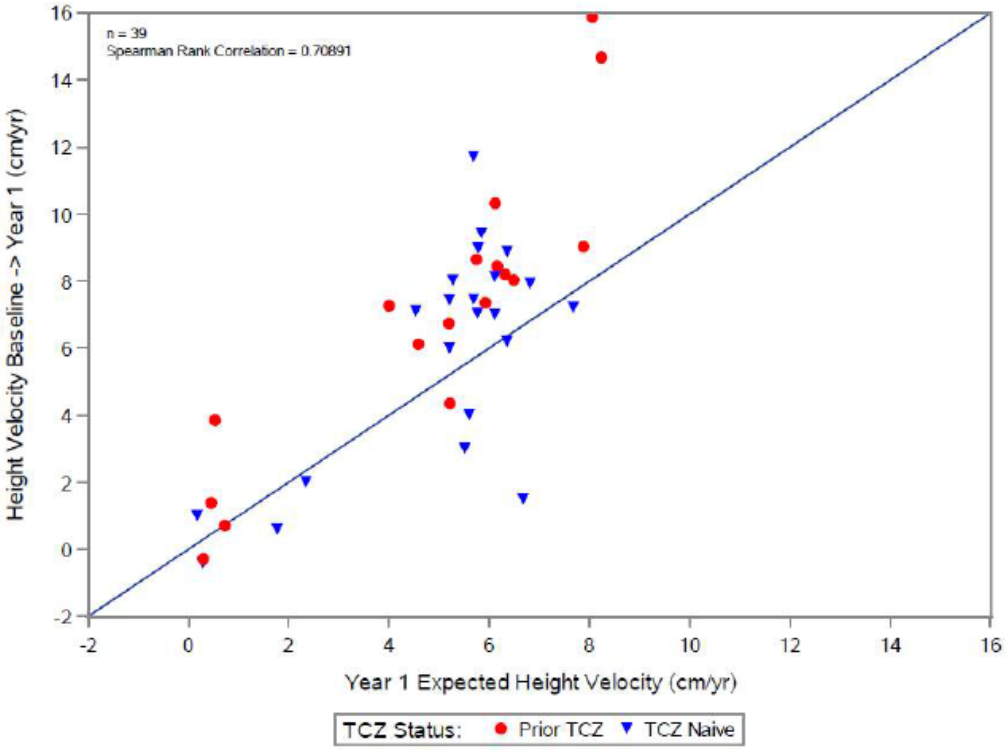
Figure 12 Plot of one-year height velocity versus baseline age by gender



Height velocity is calculated as ((height at timepoint - height at baseline) / (time between observations in days)) * 365.25
Solid line shows where WHO expected height velocity = Baseline to Year 1 height velocity.
Program: /opt/BIOSTAT/prod/cn11935d/i28118b/g_grwth_hv.sas
Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/g_grwth_hv.pdf

Figure 13 One-year height velocity against WHO expected one year height velocity

Ancillary analyses

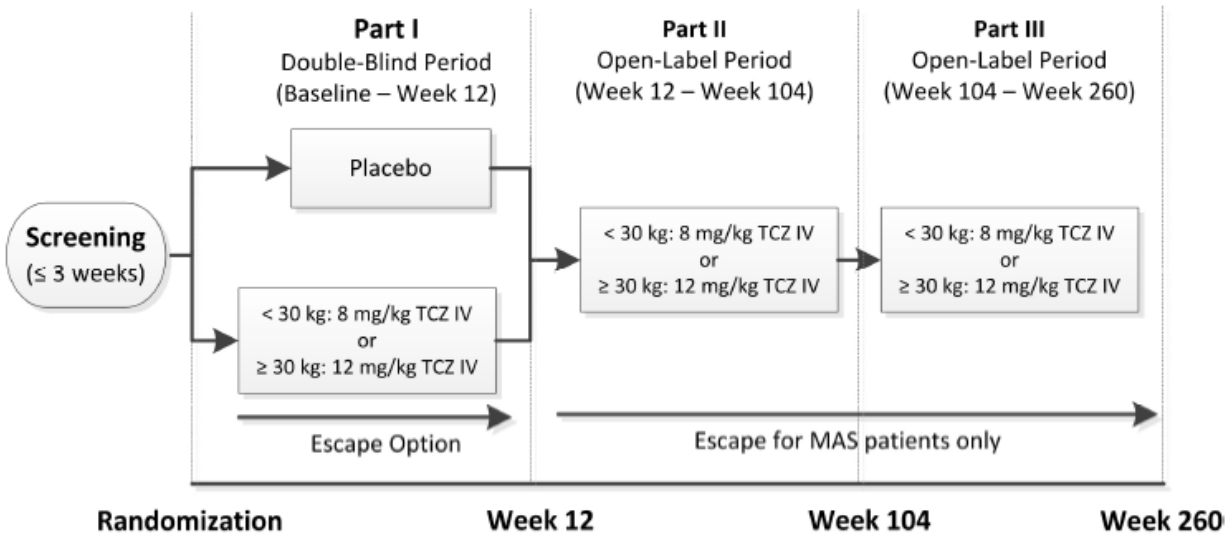
Analysis performed across trials (pooled analyses and meta-analysis) / Supportive studies

- **Study WA18221**

Study WA18221 (also known as TENDER) was a five-year, three-part Phase III study to evaluate the efficacy and safety of TCZ administered intravenously in patients over 2 years of age with active sJIA.

The study consisted of three parts:

- Part I was a 12-week placebo-controlled, double-blind and randomized phase. Eligible patients were randomized 2:1 to receive either TCZ IV or placebo IV.
- Part II consisted of a single-arm, open-label 92-week treatment phase. Patients previously receiving TCZ in Part I continued on the same dose while patients previously receiving placebo received TCZ IV at the dose based on their BW. The primary objectives of Part II were to evaluate the safety of TCZ in chronic administration and to assess the effect of TCZ to enable the reduction or elimination of corticosteroids. The primary objectives of Part I were to assess the efficacy and short-term safety of TCZ IV versus placebo in combination with stable ongoing therapy in patients with sJIA. Patients who completed the first 12 Weeks in Part I of the study had the option to enter into Part II of the study. Patients who entered escape during Part I and who were benefiting from receiving TCZ were also able to enter Part II. Patients completing Part II of the study were eligible to enter Part III.
- Part III was a single-arm, open-label 3-year study. Patients continued to receive TCZ IV at the same dose and frequency as in Part II of the study. Switching dose based on non-transient changes in BW was permitted. This part of the study also included an optional alternative TCZ dosing schedule (i.e. less frequent TCZ infusion schedules every 3 or 4 weeks [Q3W/Q4W] or no TCZ infusions) for patients who qualified based on their clinical response and safety status. The primary objective of Part III was to assess the long-term safety of TCZ IV in children.



MAS = Macrophage activation syndrome.

Figure 14 Overview study design

Patients aged 2 up to and including 17 years with sJIA with persistent activity and an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids were eligible for study enrolment.

Treatments

Part I: 12-week placebo-controlled treatment phase.

- < 30 kg randomised 2:1 to TCZ 12 mg/kg IV Q2W or placebo IV Q2W
- ≥ 30 kg randomised 2:1 to TCZ 8 mg/kg IV every 2 weeks (Q2W) or placebo IV Q2W

Patients had the option to escape the double-blind treatment and receive open lable TCZ in case of high disease burden, among other reasons.

Part II: single-arm, open-label 92-week treatment phase

- < 30 TCZ 12 mg/kg IV Q2W
- ≥ 30 kg TCZ 8 mg/kg IV Q2W

Patients could switch dosing regimen based on non-transient changes in BW (< 30 kg to ≥ 30 kg) over a minimum of 3 consecutive visits.

Reductions in corticosteroids, MTX and NSAIDs were permitted if the pre-specified criteria were met

Part III: open-label 3-year treatment phase

- < 30 TCZ 12 mg/kg IV Q2W
- ≥ 30 kg TCZ 8 mg/kg IV Q2W

Switching dose based on non-transient changes in BW was permitted. Reductions in corticosteroids, MTX and NSAIDs were permitted. This part of the study also included an optional alternative TCZ

dosing schedule (i.e., less frequent TCZ infusion schedules every 3 or 4 weeks [Q3W/Q4W] or no TCZ infusions) for patients who qualified based on their clinical response and safety status.

- **LTE study WA29231**

Study WA29231 is an ongoing open-label extension of the TCZ SC JIGSAW studies (WA28117 [pJIA] and WA28118 [sJIA]). The study recruited patients with pJIA or sJIA who had completed either JIGSAW study and had an adequate response to TCZ SC, per the clinical judgment of the investigator.

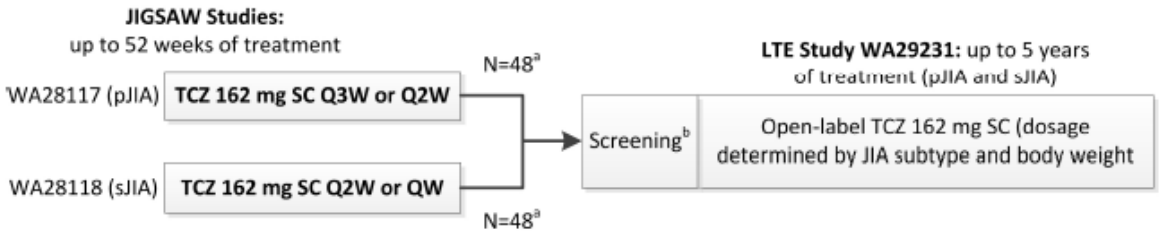
The primary objectives of the study are to assess the long-term safety and efficacy of TCZ SC in patients with pJIA and sJIA. The exploratory objectives are to explore the long-term PK and PD of TCZ SC in pJIA and sJIA patients.

Treatment

For sJIA, the same dosing regimen as determined after interim analysis in Study WA28118 is employed:

- < 30 kg: 162 mg TCZ SC Q2W (or Q10D prior to implementation of the protocol amendment following the interim analysis)
- ≥ 30 kg: 162 mg TCZ SC QW

The dosing interval could be adjusted according to changes in BW during the course of the study as specified in the protocol.



Q2W = every 2 weeks; Q3W = every 3 weeks; QW = every week; pJIA = polyarticular juvenile idiopathic arthritis; sJIA = systemic juvenile idiopathic arthritis.
Note: Following the planned WA28118 interim analysis, the dosing regimen for < 30 kg patients with sJIA initially on Q10D (n = 5) changed to Q2W dosing frequency. One patient on Q10D dosing withdrew prior to the switch in dosing frequency.

[a] Approximately 48 patients from each JIGSAW study were to be enrolled in this LTE study.

[b] Laboratory data obtained from the last dosing clinic visit or WD1 in JIGSAW could have been used for screening assessments for this study.

Figure 15 Overview study design

In this report, only interim data (11 August 2017 cut off) from sJIA patients are presented.

Results

Baseline disease characteristic and previous concomitant medication

Table 19 Comparison of key demographics and disease characteristics at baseline for TCZ SC (WA28118 and WA29231) and TCZ IV (WA18221)

	TCZ SC (WA28118)				TCZ IV (WA18221)		TCZ SC LTE (WA29231)	
	162 mg SC Q10D or Q2W (< 30 kg) N = 25		162 mg SC QW (≥ 30 kg) N = 26		12 mg/kg Q2W	8 mg/kg Q2W	162 mg SC Q10D or Q2W	162 mg SC QW
	TCZ Naive n = 15	Prior TCZ n = 10	TCZ Naive n = 11	Prior TCZ n = 15	(< 30 kg) n = 50	(≥ 30 kg) n = 52	(< 30 kg) n = 19	(≥ 30 kg) n = 19
Age (years), mean (SD)	5.2 (3.0)	4.9 (3.6)	13.1 (3.2)	13.5 (3.2)	5.9 (2.8)	13.4 (2.8)	4.9 (2.3)	13.9 (3.5)
Min – Max	2 – 13	1[a] – 10	8 – 17	6 – 17	2 – 13	7 – 17	2 – 9	7 – 18
Males, n (%)	8 (53.3%)	4 (40.0%)	5 (45.5%)	5 (33.3%)	24 (48%)	24 (46%)	9 (47.4%)	8 (42.1%)
Females, n (%)	7 (46.7%)	6 (60.0%)	6 (54.5%)	10 (66.7%)	26 (52%)	28 (54%)	10 (52.6%)	11 (57.9%)
Weight (kg), mean (SD)	19.1 (5.4)	18.1 (6.4)	52.2 (14.3)	51.3 (12.8)	18.9 (5.4)	49.2 (18.5)	19.5 (5.2)	51.1 (13.9)
Min – Max	9.2 – 27.0	10.3 – 27.2	30.0 – 73.2	33.3 – 72.9	10.0 – 29.0	30.6 – 112.7	11.5 – 28.0	30.8 – 77.1
Prior non-biologic DMARD use, n (%)	7 (46.7%)	7 (70.0%)	9 (81.8%)	15 (100.0%)	32 (64%)	39 (75%)	11 (57.9%)	18 (94.7%)
Prior biologic DMARD use, n (%)	4 (26.7%)	10 (100.0%)	8 (72.7%)	15 (100.0%)	34 (68%)	48 (92%)	15 (78.9%)	19 (100.0%)
Background oral CS use, n (%)	14 (93.3%)	6 (60.0%)	8 (72.7%)	4 (26.7%)	48 (96.0%)	45 (86.5%)	4 (21.1%)	4 (21.1%)
Background MTX use, n (%)	8 (53.3%)	5 (50.0%)	5 (45.5%)	9 (60.0%)	40 (80%)	30 (58%)	6 (31.6%)	7 (36.8%)
ESR (mm/hr), mean (SD)	38.1 (29.7)	3.1 (2.1)	31.8 (27.9)	4.2 (4.3)	59.8 (31.3)	53.8 (36.9)	5.9 (13.4)	2.5 (1.1)
CRP (mg/dL), mean (SD)	41.1 (50.5)	0.5 (0.5)	25.4 (39.2)	0.2 (0.1)	14.8 (23.7)	19.4 (45.6)	2.2 (8.4)	0.4 (0.5)
JADAS-71 (0-101), median (Min – Max)	15.1 (7.7 – 53.1)	2.5 (0.0 – 10.5)	13.2 (1.9 – 46.9)	1.0 (0.0 – 17.8)	33.8 (0.0 – 96.1)	33.3 (2.3 – 89.0)	0.40 (0.0 – 14.2)	0.25 (0.0 – 11.2)
CHAQ-DI Score (0-3), mean (SD)	1.28 (0.93)	0.28 (0.42)	0.78 (1.00)	0.45 (0.77)	1.63 (0.88)	1.75 (0.86)	0.08 (0.17)	0.16 (0.52)

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.

CHAQ-DI = Childhood Health Assessment Questionnaire Disability Index; CS = corticosteroid; DMARD = Disease-Modifying Anti-Rheumatic Drug; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; JADAS = Juvenile Arthritis Disease Activity Score; MTX = methotrexate; SD = standard deviation.

[a] 3 patients < 2 years old (17 months, 19 months, and 22 months) at baseline were recruited into the study.

Patient demographics at baseline in the TCZ SC Study WA28118 were broadly comparable with those in the TCZ IV Study WA18221 with the following notable differences in disease characteristics and previous or concomitant medication use between TCZ naive SC patients. In study WA28118 a lower proportion of TCZ naive SC patients received prior non-biologic and biologic DMARDs. In the < 30 kg BW groups (47%, 7/15 and 27%, 4/15) compared with TCZ IV patients (64%, 32/50 and 68%, 34/50), respectively. In the ≥ 30 kg BW groups, 73% (8/11) vs. 92% (48/52), respectively. TCZ naive SC patients in both BW groups had lower disease activity and slightly better physical function at baseline, as measured by median JADAS-71 and mean CHAQ-DI scores compared with TCZ IV patients.

Additionally, patients in the LTE Study WA29231 had lower disease activity (JADAS-71) and better physical function (CHAQ-DI) at baseline compared with the prior TCZ patients in WA28118, indicating overall improvement or maintenance of efficacy in the patients enrolling from WA28118 who had received a year of TCZ SC therapy.

Efficacy

The efficacy results for TCZ SC Study WA28118 were exploratory in nature as the study was not controlled, and the number of patients who were TCZ naive in WA28118 was low (n = 26). These patients are the most appropriate group for efficacy comparisons to Study WA18221, as all patients in the IV study were TCZ naive. At week 52 of the 112 patients in the LTE data cut of Study WA18221, a total of 88 patients had JADAS-71 assessments and 83 patients had pain VAS and CHAQ-DI assessments.

Table 20 Comparison of TCZ SC (WA28118) and TCZ IV (WA18221 LTE) JADAS-71 results

	TCZ Naive SC (WA28118)			TCZ IV (WA18221)		
	162 mg Q10D or Q2W (<30 kg)	162 mg QW (≥30 kg)	All TCZ Naive	12 mg/kg Q2W (<30 kg)	8 mg/kg Q2W (≥ 30 kg)	All TCZ [a]
JADAS-71	**n = 15**	**n = 11**	**n = 26**	**n = 50**	**n = 52**	**n = 112**
Baseline	n = 15	n = 11	n = 26	n = 50	n = 52	n = 112
Median	15.10	13.20	14.85	33.75	33.25	32.40
(min – max)	(7.7 – 53.1)	(1.9 – 46.9)	(1.9 – 53.1)	(0.0 – 96.1)	(2.3 – 89.0)	(0.0 – 96.1)
Mean (SD)	23.60 (15.59)	15.90 (12.43)	20.34 (14.59)	35.06 (18.22)	38.22 (19.62)	35.98 (18.59)
Week 10	n = 14	n = 11	n = 25	n = 50	n = 52	n = 112
Median	3.25	2.00	3.20	7.95	8.85	7.95
(min – max)	(0.4 – 36.3)	(0.0 – 13.9)	(0.0 – 36.3)	(0.0 – 43.2)	(0.0 – 75.5)	(0.0 – 75.5)
Mean (SD)	7.86 (11.78)	4.34 (4.65)	6.31 (9.35)	8.85 (7.56)	14.74 (17.02)	11.60 (13.34)
Week 30	n = 14	n = 11	n = 25	n = 47	n = 51	n = 108
Median	1.10	1.30	1.30	3.20	4.80	3.80
(min – max)	(0.0 – 12.0)	(0.1 – 18.4)	(0.0 – 18.4)	(0.0 – 32.3)	(0.0 – 56.8)	(0.0 – 56.8)
Mean (SD)	1.94 (3.12)	4.07 (5.59)	2.88 (4.41)	5.47 (6.98)	9.31 (12.37)	7.10 (9.90)
Week 52	n = 12	n = 11	n = 23	n = 38	n = 44	n = 88
Median	0.30	0.20	0.20	1.60	3.20	2.75
(min – max)	(0.0 – 6.0)	(0.0 – 5.7)	(0.0 – 6.0)	(0.0 – 14.8)	(0.0 – 46.8)	(0.0 – 46.8)
Mean (SD)	1.31 (1.83)	1.25 (1.73)	1.28 (1.74)	3.57 (4.15)	6.79 (10.51)	5.18 (8.09)

WA28118: LOCF applied to missing core components at visits. WA18221 LTE: Each visit includes patients with a non-missing assessment at the time point.
[a] The 'All TCZ' group presented for WA18221 has an n = 112 because it includes patients who switched from one of the two TCZ doses during the study; these 'switcher' groups 'TCZ 8 mg/kg to TCZ 12 mg/kg' n = 1 and 'TCZ 12 mg/kg to TCZ 8 mg/kg' n = 9 are not shown.

JADAS-71 results in TCZ SC patients followed a similar trend as those observed with TCZ IV. Progressive improvements in JADAS-71 through Week 52 were observed for both TCZ naive SC and TCZ IV patients. The median values at Week 52 remained slightly lower in TCZ naive SC patients (0.20, below the inactive disease threshold of < 1.0) when compared to TCZ IV patients (2.75, below the minimal disease activity threshold of < 3.8).

Pain VAS

Table 21 Comparison of TCZ SC (WA28118) and TCZ IV (WA18221) pain VAS

	TCZ Naive SC (WA28118)			TCZ IV (WA18221)		
Pain VAS (mm)	162 mg Q10D or Q2W (< 30 kg) n = 15	162 mg QW (≥ 30 kg) n = 11	All TCZ Naive n = 26	12 mg/kg Q2W (< 30 kg) n = 50	8 mg/kg Q2W (≥ 30 kg) n = 52	All TCZ [a] n = 112
Baseline	15	11	26	50	52	112
Median	57.0	32.0	50.0	60.0	67.5	63.5
(min – max)	(5 – 91)	(1 – 84)	(1 – 91)	(0 – 95)	(0 – 100)	(0 – 100)
Mean (SD)	52.5 (30.1)	32.0 (30.5)	43.8 (31.4)	54.7 (26.2)	62.6 (24.8)	58.7 (25.8)
Week 10	13	10	23	50	51	111
Median	16.0	11.0	14.0	10.5	21.0	14.0
(min – max)	(0 – 50)	(0 – 39)	(0 – 50)	(0 – 72)	(0 – 89)	(0 – 89)
Mean (SD)	19.2 (19.4)	15.8 (16.1)	17.7 (17.7)	14.2 (15.8)	29.4 (26.1)	21.7 (22.2)
Week 30	14	11	25	46	49	104
Median	2.0	11.0	4.0	3.0	10.0	6.0
(min – max)	(0 – 37)	(0 – 80)	(0 – 80)	(0 – 82)	(0 – 89)	(0 – 89)
Mean (SD)	8.6 (12.2)	15.0 (22.8)	11.4 (17.5)	11.3 (18.2)	18.0 (21.6)	14.4 (19.6)
Week 52	10	11	21	36	41	83
Median	0.0	2.0	1.0	3.0	5.0	4.0
(min – max)	(0 – 27)	(0 – 15)	(0 – 27)	(0 – 39)	(0 – 69)	(0 – 69)
Mean (SD)	3.6 (8.5)	4.5 (5.7)	4.0 (7.0)	7.6 (10.8)	12.1 (16.8)	10.3 (14.5)

IV = intravenous; Q10D = every 10 days; Q2W = every 2 weeks; QW = every week; SC = subcutaneous; TCZ = tocilizumab.

[a] The 'All TCZ' group presented for WA18221 has an n = 112 because it includes patients who switched from one of the two TCZ doses during the study; these 'switcher' groups 'TCZ 8 mg/kg to TCZ 12 mg/kg' n = 1 and 'TCZ 12 mg/kg to TCZ 8 mg/kg' n = 9 are not shown.

Mean pain VAS results in TCZ SC patients followed a similar trend as those observed with TCZ IV. In the All TCZ groups, TCZ naive SC patients had slightly lower mean (± SD) pain VAS values at baseline compared with TCZ IV patients (43.8 ± 31.4 mm vs. 58.7 ± 25.8 mm). Progressive improvements in pain VAS results through Week 52 were observed for both TCZ naive SC and TCZ IV patients. The mean values at Week 52 remained slightly lower in TCZ naive SC patients when compared with TCZ IV patients (4.0 ± 7.0 mm vs. 10.3 ± 14.5 mm).

By BW group, TCZ naive SC patients in the < 30 kg BW group had a similar mean baseline pain VAS results compared with TCZ IV patients of the same BW group (52.5 ± 30.1 mm vs. 54.7 ± 26.2 mm), and thereafter followed a similar decrease through Week 52 (3.6 ± 8.5 mm vs. 7.6 ± 10.8 mm). In contrast, TCZ naive SC patients in the ≥ 30 kg BW group had a lower mean baseline pain VAS values compared with TCZ IV patients of the same BW group (32.0 ± 30.5 mm vs. 62.6 ± 24.8 mm), which remained lower through Week 52 (4.5 ± 5.7 mm vs. 12.1 ± 16.8 mm).

CHAQ-DI

Table 22 Comparison of TCZ SC (WA28118) and TCZ IV (WA18221) CHAQ-DI

	TCZ Naive SC (WA28118)			TCZ IV (WA18221)		
	162 mg Q10D or Q2W (< 30 kg)	162 mg QW (≥ 30 kg)	All TCZ Naive	12 mg/kg Q2W (< 30 kg)	8 mg/kg Q2W (≥ 30 kg)	All TCZ [a]
CHAQ-DI	**n = 15**	**n = 11**	**n = 26**	**n = 50**	**n = 52**	**n = 112**
Baseline	15	11	26	50	52	112
Median	1.50	0.25	0.88	1.75	1.88	1.75
(min – max)	(0.00 – 2.50)	(0.00 – 2.63)	(0.00 – 2.63)	(0.00 – 3.00)	(0.00 – 3.00)	(0.00 – 3.00)
Mean (SD)	1.28 (0.93)	0.78 (1.00)	1.07 (0.97)	1.63 (0.87)	1.75 (0.86)	1.68 (0.86)
Week 10	13	10	23	50	51	111
Median	0.25	0.06	0.13	0.63	1.00	0.88
(min – max)	(0.00 – 1.75)	(0.00 – 2.38)	(0.00 – 2.38)	(0.00 – 2.75)	(0.00 – 2.88)	(0.00 – 2.88)
Mean (SD)	0.38 (0.56)	0.33 (0.74)	0.35 (0.63)	0.83 (0.70)	1.19 (0.90)	1.02 (0.83)
Week 30	14	11	25	45	49	103
Median	0.06	0.00	0.00	0.25	0.75	0.50
(min – max)	(0.00 – 0.88)	(0.00 – 2.25)	(0.00 – 2.25)	(0.00 – 2.00)	(0.00 – 2.75)	(0.00 – 2.75)
Mean (SD)	0.24 (0.32)	0.49 (0.77)	0.35 (0.56)	0.60 (0.70)	0.92 (0.85)	0.76 (0.80)
Week 52	10	11	21	35	42	83
Median	0.00	0.00	0.00	0.25	0.50	0.38
(min – max)	(0.00 – 0.13)	(0.00 – 1.88)	(0.00 – 1.88)	(0.00 – 2.13)	(0.00 – 2.88)	(0.00 – 2.88)
Mean (SD)	0.01 (0.04)	0.25 (0.56)	0.14 (0.41)	0.52 (0.64)	0.82 (0.83)	0.69 (0.77)

CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; IV = intravenous; Q10D = every 10 days; Q2W = every 2 weeks; QW = every week; SC = subcutaneous; TCZ = tocilizumab.

[a] The 'All TCZ' group presented for WA18221 has an n = 112 because it includes patients who switched from one of the two TCZ doses during the study; these 'switcher' groups 'TCZ 8 mg/kg to TCZ 12 mg/kg' n = 1 and 'TCZ 12 mg/kg to TCZ 8 mg/kg' n = 9 are not shown.

In the All TCZ groups, TCZ naive SC patients had slightly lower mean CHAQ-DI scores at baseline compared with TCZ IV patients (1.07 + 0.97 vs. 1.68 + 0.86). Progressive improvements in mean CHAQ-DI scores through Week 52 were observed for TCZ naive SC (- 90.8% mean CFB) and TCZ IV patients (- 57.2% mean CFB). The mean scores at Week 52 remained slightly lower in TCZ naive SC patients when compared with TCZ IV patients (0.14 + 0.41 vs. 0.69 + 0.77). The same observations also applied when comparing TCZ naive SC and TCZ IV patients within the < 30 kg and > 30 kg BW groups

Growth

Since height SDS was not evaluated in the LTE data cut of Study WA18221, the comparison is made with data from the 104-Week WA18221 CSR.

No TCZ naive SC patients (WA28118) took the growth hormone somatotropin during the study. TCZ IV (WA18221) patients taking somatropin were excluded from the growth analysis.

Table 23 Comparison of TCZ SC (WA28118) and TCZ IV (WA18221) Height Standard Deviation Results

	TCZ Naive SC (WA28118)		TCZ IV (WA18221)	
Standard Deviation Scores (SDS)	162 mg Q10D or Q2W (< 30 kg) n = 15	162 mg QW (≥ 30 kg) n = 11	12 mg/kg Q2W (< 30 kg) n = 39	8 mg/kg Q2W (≥ 30 kg) n = 48
Baseline	15	11	39	48
Median	–1.07	0.53	–1.88	–1.26
(min - max)	(–3.8 - 2.7)	(–3.9 - 1.1)	(–6.43 - 0.53)	(–6.48 - 1.98)
Mean (SD)	–1.22 (1.69)	–0.26 (1.54)	–2.10 (1.81)	–1.77 (2.05)
Month 6	14	11	37	47
Median	–1.06	0.47	–1.50	–1.23
(min - max)	(–3.7 - 2.2)	(–3.9 - 1.0)	(–6.25 - 0.30)	(–6.58 - 1.78)
Mean (SD)	–1.16 (1.46)	–0.31 (1.55)	–1.90 (1.77)	–1.78 (1.97)
Year 1	13	11	34	44
Median	–0.55	0.27	–1.26	–1.12
(min - max)	(–2.4 - 0.9)	(–3.8 - 1.0)	(–6.15 - 0.57)	(–6.26 - 2.14)
Mean (SD)	–0.77 (1.03)	–0.32 (1.57)	–1.69 (1.76)	–1.57 (1.90)

IV = intravenous; Q10D = every 10 days; Q2W = every 2 weeks; QW = every week; SC = subcutaneous; SDS = standard deviation score; TCZ = tocilizumab.

TCZ naive SC patients in both BW groups had baseline mean height SDS values closer to the reference value (0) compared with TCZ IV patients. Mean height SDSs improved through Year 1 for TCZ naive SC and TCZ IV patients in the < 30 kg BW group, and for TCZ IV patients in the > 30 kg BW group. TCZ naive SC patients in the > 30 kg BW group had stable mean height SDS through Week 52.

Long-term extension efficacy data from WA29231

Supportive LTE efficacy data are provided from 38 patients with sJIA who were enrolled in Study WA29231 at the time of the clinical cut-off date (11 August 2017). This LTE population provides additional median treatment duration of 0.31 years for patients in the < 30 kg BW group and 2.30 years for patients in the > 30 kg BW group.

Table 24 Summary of Efficacy Results

	JADAS-71			Inactive Disease [a]			Clinical Remission [b]			CHAQ-DI		
	162 mg Q10D or Q2W (< 30 kg)	162 mg QW (≥ 30 kg)	All	162 mg Q10D or Q2W (< 30 kg)	162 mg QW (≥ 30 kg)	All	162 mg Q10D or Q2W (< 30 kg)	162 mg QW (≥ 30 kg)	All	162 mg Q10D or Q2W (< 30 kg)	162 mg QW (≥ 30 kg)	All
	n = 19	n = 19	n = 38	n = 19	n = 19	n = 38	n = 19	n = 19	n = 38	n = 19	n = 19	n = 38
Baseline	n = 17	n = 18	n = 35	n = 17	n = 18	n = 35				n = 17	n = 19	n = 36
Median / %[c]	0.40	0.25	0.30	76.5%	83.3%	80.0%				0.00	0.00	0.00
(min – max)	0.0 – 14.2	0.0 – 11.2	0.0 – 14.2							(0.00 – 0.50)	(0.00 – 2.25)	(0.00 – 2.25)
Mean (SD)	1.72 (3.56)	1.39 (2.71)	1.55 (3.11)							0.08 (0.17)	0.16 (0.52)	0.13 (0.39)
Week 8	n = 13	n = 18	n = 31	n = 13	n = 18	n = 31				n = 13	n = 18	n = 31
Median / %[c]	0.50	0.20	0.30	69.2%	83.3%	77.4%				0.00	0.00	0.00
(min – max)	0.0 – 27.5	0.0 – 14.2	0.0 – 27.5							(0.00 – 0.88)	(0.00 – 1.75)	(0.00 – 1.75)
Mean (SD)	2.97 (7.48)	1.32 (3.30)	2.01 (5.41)							0.19 (0.27)	0.16 (0.43)	0.17 (0.36)
Week 16[d]	n = 10	n = 19	n = 29	n = 10	n = 19	n = 29	n = 8	n = 19	n = 27	n = 8	n = 19	n = 27
Median / %[c]	0.05	0.10	0.10	90.0%	94.7%	93.1%	62.5%	57.9%	59.3%	0.00	0.00	0.00
(min – max)	0.0 – 3.4	0.0 – 5.8	0.0 – 5.8							(0.00 – 0.43)	(0.00 – 2.00)	(0.00 – 2.00)
Mean (SD)	0.45 (1.05)	0.95 (1.62)	0.78 (1.45)							0.07 (0.15)	0.18 (0.48)	0.15 (0.41)
Week 56	n = 5	n = 12	n = 17	n = 5	n = 12	n = 17	n = 5	n = 12	n = 17	n = 5	n = 12	n = 17
Median / %[c]	0.30	0.10	0.10	60.0%	83.3%	76.5%	60.0%	66.7%	64.7%	0.00	0.00	0.00
(min – max)	0.0 – 12.2	0.0 – 5.2	0.0 – 12.2							(0.00 – 0.38)	(0.00 – 2.13)	(0.00 – 2.13)
Mean (SD)	3.76 (5.43)	0.69 (1.48)	1.59 (3.31)							0.13 (0.18)	0.22 (0.62)	0.19 (0.52)
Week 96	n = 4	n = 12	n = 16	n = 4	n = 12	n = 16	n = 4	n = 12	n = 16	n = 3	n = 12	n = 15
Median / %[c]	0.10	0.30	0.15	75.0%	75.0%	75.0%	50.0%	75.0%	68.8%	0.00	0.00	0.00
(min – max)	0.0 – 3.2	0.0 – 3.8	0.0 – 3.8							(0.00 – 0.13)	(0.00 – 1.75)	(0.00 – 1.75)
Mean (SD)	0.85 (1.57)	0.73 (1.12)	0.76 (1.19)							0.04 (0.07)	0.20 (0.51)	0.17 (0.46)
Week 128	n = 1	n = 8	n = 9	n = 1	n = 8	n = 9	n = 1	n = 8	n = 9	n = 1	n = 6	n = 7
Median / %[c]	0.30	0.05	0.10	100%	100%	100%	100%	87.5%	88.9%	0.00	0.00	0.00
(min – max)	0.30 – 0.30	0.0 – 1.5	0.0 – 1.5							0.00 – 0.00	0.00 – 0.00	0.00 – 0.00
Mean (SD)	0.30 (-)	0.29 (0.51)	0.29 (0.48)							0.00 (-)	0.00 (0.00)	0.00 (0.00)

IV = intravenous; CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; JADAS-71 = Juvenile Arthritis Disease Activity Score 71; LTE = long-term extension; Q2W = every 2 weeks; QW = every week; SC = subcutaneous; TCZ = tocilizumab; *NA* = not applicable; TCZ = tocilizumab.

[a] Inactive disease is defined as no presence of active joints, no fever or physical exam features [including active uveitis] attributable to sJIA, a physician global VAS ≤ 10 mm, and a normal ESR [< 20 mm/hr]).

[b] Clinical remission is defined as inactive disease for a minimum of 6 continuous months irrespective of disease-modifying anti-rheumatic drug, nonsteroidal anti-inflammatory drug, or corticosteroid use.

[c] Median for JADAS-71 and CHAQ-DI, percentage (%) for inactive disease and clinical remission.

[d] Week 24 for clinical remission.

Of the 19 patients in the < 30 kg BW group, 6 patients (31.6%) entered Study WA29231 on a Q10D dosing regimen that started in Study WA28118. These patients had a treatment duration between 0.4 - 2.6 years in WA29231 (i.e. a total of approximately 1.4 - 3.6 years on TCZ SC therapy from WA28118 and WA29231 combined) at the time of the clinical cut-off date. Five of the 6 patients were switched from the Q10D dosing regimen to the Q2W dosing regimen over the course of the study. The remaining 13 patients (68.4%) who enrolled into Study WA28118 after the switch in dosing regimen

and had been receiving Q2W doses of TCZ SC, had a treatment duration between 0.0 - 0.7 years in Study WA29231 (i.e., approximately 1 - 1.7 years in both studies combined).

The 19 patients in the > 30 kg BW group had treatment duration between 0.7 - 2.9 years (i.e. approximately a total of 1.7 - 3.9 years).

Efficacy achieved with TCZ SC in study WA28118 was maintained in LTE study WA29231. Low median JADAS-71 results were maintained from the beginning through Week 16 and Week 128 of the LTE Study WA29231 for patients in the < 30 kg BW group and > 30 kg BW group, respectively (last time points when approximately half of the enrolled patients completed the efficacy assessments). The medians in JADAS-71 were below the inactive disease cut-off (< 1) for both BW groups through Week 16 (< 30 kg BW group) and Week 128 (> 30 kg BW group). The proportion of patients who achieved inactive disease and the mean CHAQ-DI scores were generally similar from baseline up to Week 16 (< 30 kg BW group) or Week 128 (< 30 kg BW group), and the proportion of patients in clinical remission (> 30 kg BW group only) increased through Week 128.

Clinical studies in special populations

No formal subpopulations were analysed in Study WA28118 due to the small patient numbers and because efficacy was exploratory.

However, since the MAH is seeking an indication for TCZ SC for sJIA patients > 1 year of age data for patients below 1 years of age are analysed separately. Three patients were under the age of 2 years at baseline in Study WA28118:

- A boy aged 17 months with a BW of 10.3 kg on Q10D regimen.
- A girl aged 19 months with a BW of 11.0 kg on Q2W regimen.
- A girl aged 22 months with a BW of 11.5 kg on Q2W regimen.

The lowest BW patient in WA28118 was a girl aged 25 months weighing 9.2 kg at baseline.

Table 25 Efficacy (JADAS-71) results of patients < 2 years old and the lightest patient in WA28118

			JADAS-71 in WA28118			
Patient No.	BW	TCZ Status	Baseline	Week 10	Week 26	Week 52
< 2 years old						
[redacted]	10.3 kg	prior TCZ	1.0	1.1	0.6	0.4
[redacted]	11.0 kg	prior TCZ	0.0	0.0	0.0	0.0
[redacted]	11.5 kg	prior TCZ	0.8	0.3	0.4	0.0
<10 kg BW at baseline						
[redacted]	9.2 kg	TCZ naive	12.0	0.4	0.2	0.0 [a]

a The JADAS-71 assessment for Week 52 has been windowed into Week 50 due to the Q10D dosing schedule for patient 257492/118031.

The JADAS-71 results for patients < 2 years old and the lightest patient (< 10 kg) in Study WA28118 showed that TCZ SC improved or maintained already low baseline JADAS-71 (0.0 - 1.0) over the course of the study (Week 52: 0.0 - 0.4). All 4 patients completed Study WA28118 and enrolled into the LTE Study WA29231.

2.4.2. Discussion on clinical efficacy

Study WA28118 is a Phase Ib, open-label, multicentre study to investigate the pharmacokinetics, pharmacodynamics, and safety of TCZ SC in patients with systemic juvenile idiopathic arthritis. The main objectives of the study were to characterize the PK, PD, and the safety of TCZ SC in patients with sJIA. Description of the efficacy of TCZ SC in patients with pJIA was an exploratory objective of the study.

Furthermore a comparative analysis of the data of TCZ SC efficacy data from the TCZ naïve patients (n = 26) through Week 52 from Study WA28118 compared with TCZ IV efficacy through Week 52 from Study WA18221 (n = 112) is included in this MAA.

The supportive study WA18221 was the pivotal study to support the paediatric indication "systemic juvenile idiopathic arthritis" (sJIA). The interim data were assessed in context of the Type II variation EMA/H/C/955/15 and the final CSR was assessed in context of MEA 34.2.

Supportive efficacy data are also derived from Study WA29231. The study population consists of patients who had completed the Study WA28117 (pJIA) or Study WA28118 study (sJIA), and had an adequate response to TCZ SC therapy. The efficacy objective for WA29231 was to assess the long-term efficacy of TCZ SC in patients with pJIA and sJIA. However, only the data from sJIA patients were presented.

Design and conduct of clinical studies

In the TCZ IV Study WA18221, all patients enrolled were TCZ naive per protocol, whereas in the TCZ SC Study WA28118, 25 out of 51 patients overall (49%) were receiving TCZ IV before enrolling into the study. Thus the 'TCZ naive' dosing groups in the TCZ SC WA28118 study are included in the comparison to the TCZ IV WA18221 study population. This approach is appropriate.

Of note, TCZ IV patients, especially those ≥30 kg, entered Study WA18221 with higher disease activity (JADAS-71) and pain scores (parent/patient pain VAS), and worse physical function (higher CHAQ-DI) compared to the TCZ SC patients entering Study WA28118.

Study WA28118 planned to enrol approximately 48 patients (actual n = 51), of which no more than 50% should have switched from commercially available TCZ IV to TCZ SC at baseline.

The target population was paediatric patients aged 1 year (12 years for patients in Russia) up to and including 17 years with a diagnosis of sJIA who had an inadequate response to NSAIDs and corticosteroids. The key inclusion and exclusion criteria for the TCZ SC Study WA28118 were generally the same as in the TCZ IV Study WA18221, with the exception that the minimum enrolment age was lowered from 2 years to 1 year in the SC study. Furthermore, in the TCZ SC Study WA28118 patients with prior TCZ IV treatment were eligible, whereas all patients were TCZ naive for the earlier pivotal TCZ IV Study WA18221.

Patients received TCZ SC according to their body weight (BW), with patients weighing > 30 kg (planned n = 24, actual n = 26) receiving 162 mg doses QW and patients weighing < 30 kg (planned n = 24, actual n = 25) receiving 162 mg doses every 10 days (Q10D) or Q2W. In the original protocol the dose regimen for patients weighing < 30 kg was Q10D. Following review of the data from the planned interim analysis of the first 28 patients who completed Week 14 of the study, the dosing regimen for patients weighing < 30 kg was changed from Q10D to Q2W. This change was applicable to all newly enrolled patients weighing < 30 kg, and in principle as well to patients weighing < 30 kg already enrolled in the study and receiving Q10D as per the initial dosing regimen. In reality, all

patients < 30 kg treated Q10D finished the treatment period before this change could be applied. In the original protocol (up to Version 5), it was further planned to replace patients treated with a different dose than finally chosen. This was revised in the final protocol (Version 6) with the result that 8 of 25 patients were treated with the more frequent dosing regimen.

Concurrent treatment with DMARDs, and oral corticosteroids was permitted at the discretion of the investigator. Immunosuppressants such as cyclosporine and cyclophosphamide, and biologic agents other than TCZ were prohibited during the study.

Description of the efficacy of TCZ SC in patients with sJIA was an exploratory objective of the study. Juvenile Arthritis Disease Activity Score (JADAS)-71, inactive disease and clinical remission and Childhood Health Assessment Questionnaire (CHAQ) were used as efficacy measures.

Of note, in the TCZ IV Study WA19977, the JIA ACR response was used as the primary efficacy endpoint measure. However the TCZ SC Study WA28117, JADAS-71 was used instead of the JIA ACR responses because it has the advantage of not relying on the change from baseline. A change from baseline based response measure would not be appropriate to evaluate maintenance of response from patients who switched from TCZ IV. JADAS-71 data were also collected in the TCZ IV Study WA19977 (104-Week WA19977 CSR).

The development program TCZ SC in sJIA is in general acceptable. Of note, the same approach was taken for the development of TCZ SC for patients with pJIA.

Efficacy data and additional analyses

Overall, the interpretation of the results is hampered by the small overall sample sizes, as well as the sample size in subgroups. Of note, at interim there were less than 50% TCZ naïve patients in the < 30 kg cohort (3 of 8) and for the final analysis there were less than 50% TCZ naïve patients in the >30 kg cohort. These exploratory data are considered supportive in addition to the pharmacological data. Further the efficacy of TCZ in the treatment pJIA was confirmed with TCZ IV. Thus, the small sample size in this context is not a concern.

JADAS-71 scores generally improved (decreased) over the course of the study for patients initiating TCZ treatment (TCZ naive patients), and were maintained or improved further for patients who switched from TCZ IV to TCZ SC (prior TCZ patients), irrespective of BW group (i.e., < 30 kg or > 30 kg).

In TCZ naive patients, the median JADAS-71 decreased from baseline to Week 52 by 13.90 for patients in the < 30 kg BW group and 12.40 for patients in the > 30 kg BW group. In these TCZ naive patients, the median JADAS-71 value reduced to the level of inactive disease (< 1.0) by Week 26 in both BW groups, and generally remained at this level for rest of the study. Prior TCZ patients had lower baseline JADAS-71 values compared with TCZ naive patients in both BW groups, and the low values were maintained below the level of minimal disease activity. Thus, patients who entered the study previously receiving TCZ IV treatment were able to maintain disease control, as reflected by JADAS-71.

An overall improvement (decrease) in mean pain VAS from baseline to Week 52 was observed in TCZ naive patients (both BW groups). In prior TCZ patients (both BW groups), the already low mean pain VAS at baseline was generally maintained throughout the study, and slightly improved by Week 52. Patients with prior TCZ use had lower mean pain VAS at baseline (< 30 kg: 11.8 mm; > 30 kg: 15.5 mm) compared with TCZ naive patients. The already low mean pain VAS at baseline was generally maintained throughout the study and slightly improved by Week 52 for both BW groups.

Inactive disease was defined as no joints with active arthritis, no fever or physical exam features (including active uveitis) attributable to sJIA, a physician global VAS < 10 mm, and a normal ESR (< 20 mm/hr), duration of morning stiffness < 15 minute. An increasing proportion of patients had inactive disease over the course of the study, irrespective of TCZ status or BW group. By Week 52, 66.7% (16/24) of TCZ naive patients and 95.0% (19/20) of prior TCZ patients had inactive disease.

Clinical remission was defined as 'inactive disease for a minimum of 6 continuous months irrespective of DMARD, NSAID or corticosteroid use'. An increasing proportion of TCZ naive patients achieved clinical remission over the course of the study, irrespective of BW group. By Week 52, 50.0% (12/24) of TCZ naive patients and 75.0% (15/20) of prior TCZ patients were in clinical remission.

The CHAQ-DI consists of 30 questions within eight domains (dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities) as well as the patient's (or parent's) global evaluation of their (child's) current disease activity and pain, both measured on a 100 mm VAS. The overall CHAQ-DI ranges from 0 (best) to 3 (worst). In TCZ naive patients, improvements in mean CHAQ-DI scores from baseline to Week 52 were observed in both BW groups. In the prior TCZ patients, improvements in mean CHAQ-DI scores from baseline to Week 52 were observed in the > 30 kg BW group, while for the < 30 kg BW group, the mean CHAQ-DI scores were maintained around the already low baseline value during the study.

The MAH was asked to comment on the somehow weaker performance of SC TCZ in TCZ naïve patients in above 30kg BW group. The CHMP endorsed the MAH's response explaining the difficulties to interpret the efficacy results. Indeed, there were only 15 patients in the TCZ naive <30 kg group, 10 patients in the Prior TCZ <30 kg group, 11 patients in the TCZ naive ≥30 kg group, and 15 patients in the Prior TCZ ≥30 kg group at baseline, with the number of evaluable patients in the efficacy analyses sometimes lower across visits due to missing data or dropouts. With such small patient numbers, inter-patient variability can strongly influence the results, making it difficult to draw robust conclusions for these four patient subgroups.

Tanner stage was not collected in this study. Therefore, the > 30 kg BW group includes patients who had reached puberty and attained their final adult height, creating bias within this group. At baseline, the mean height SDS of TCZ naive patients in the < 30 kg BW group was below the normal reference range, and increased at Month 6 and Year 1 in this group, indicating improvement from baseline towards the normal reference height. Mean baseline height SDSs for the other three subgroups (TCZ naive in the > 30 kg BW group and prior TCZ patients in both BW groups) were closer to the normal reference height at baseline, and showed increases or remained stable over the 12 month period, indicating minor improvement or normal growth. Overall, individual patient's height SDSs remained mostly stable or improved over the course of the study.

Results from exploratory endpoints showed that TCZ SC improved (TCZ naïve patients) or maintained (prior TCZ patients) efficacy for all parameters evaluated over the course of the study for patients in both BW groups (< 30 kg and > 30 kg).

Comparative efficacy analysis of the TCZ SC efficacy data (Study WA 28118) with TCZ IV (Study WA19977) was provided. The analysis compared TCZ naïve patients (n = 37) through Week 52 from Study WA28117 with TCZ IV efficacy data from the "continuous TCZ" IV subgroup (n = 82) through Week 52 from Study WA19977.

Furthermore a comparative analysis of the data of TCZ SC efficacy data from the TCZ naïve patients (n = 26) through Week 52 from Study WA28118 compared with TCZ IV efficacy through Week 52 from Study WA18221 (n = 112) was included in this MAA.

Patient demographics at baseline in the TCZ SC Study WA28118 were broadly comparable with those in the TCZ IV Study WA18221 with the following notable differences in disease characteristics and previous or concomitant medication use between TCZ naive SC patients. In study WA28118 a lower proportion of TCZ naive SC patients received prior non-biologic and biologic DMARDs. In the < 30 kg BW groups (47%, 7/15 and 27%, 4/15) compared with TCZ IV patients (64%, 32/50 and 68%, 34/50), respectively. In the > 30 kg BW groups, 73% (8/11) vs. 92% (48/52), respectively. TCZ naive SC patients in both BW groups had lower disease activity and slightly better physical function at baseline, as measured by median JADAS-71 and mean CHAQ-DI scores compared with TCZ IV patients.

JADAS-71 results in TCZ SC patients followed a similar trend as those observed with TCZ IV. Progressive improvements in JADAS-71 through Week 52 were observed for both TCZ naive SC and TCZ IV patients. The median values at Week 52 remained slightly lower in TCZ naive SC patients (0.20, below the inactive disease threshold of < 1.0) when compared to TCZ IV patients (2.75, below the minimal disease activity threshold of < 3.8. By BW group, similar efficacy trends between TCZ naive SC and TCZ IV were also observed.

Mean pain VAS results in TCZ SC patients followed a similar trend as those observed with TCZ IV. In the All TCZ groups, TCZ naive SC patients had slightly lower mean pain VAS values at baseline compared with TCZ IV patients. Progressive improvements in pain VAS results through Week 52 were observed for both TCZ naive SC and TCZ IV patients. By BW group, TCZ naive SC patients in the < 30 kg BW group had a similar mean baseline pain VAS results compared with TCZ IV patients of the same BW group, and thereafter followed a similar decrease through Week 52. In contrast, TCZ naive SC patients in the > 30 kg BW group had a lower mean baseline pain VAS result compared with TCZ IV patients of the same BW group, which remained lower through Week 52.

In the All TCZ groups, TCZ naive SC patients had slightly lower mean CHAQ-DI scores at baseline compared with TCZ IV patients. Progressive improvements in mean CHAQ-DI scores through Week 52 were observed for TCZ naive SC and TCZ IV patients. The mean scores at Week 52 remained slightly lower in TCZ naive SC patients when compared with TCZ IV patients. The same observations also applied when comparing TCZ naive SC and TCZ IV patients within the < 30 kg and > 30 kg BW groups.

TCZ naive SC patients in both BW groups had baseline mean height SDS values closer to the reference value (0) compared with TCZ IV patients. Mean height SDSs improved through Year 1 for TCZ naive SC and TCZ IV patients in the < 30 kg BW group, and for TCZ IV patients in the > 30 kg BW group. TCZ naive SC patients in the > 30 kg BW group had stable mean height SDS through Week 52.

Supportive LTE efficacy data are provided from 38 patients with sJIA who were enrolled in Study WA29231 at the time of the clinical cut-off date (11 August 2017). This LTE population provides additional median treatment duration of 0.31 years for patients in the < 30 kg BW group and 2.30 years for patients in the > 30 kg BW group.

Efficacy achieved with TCZ SC in Study WA28118 was maintained in LTE study WA29231. Low median JADAS-71 results were maintained from the beginning through Week 16 and Week 128 of the LTE Study WA29231 for patients in the < 30 kg BW group and > 30 kg BW group, respectively (last time points when approximately half of the enrolled patients completed the efficacy assessments). The medians in JADAS-71 were below the inactive disease cut-off (< 1) for both BW groups through Week 16 (< 30 kg BW group) and Week 128 (> 30 kg BW group). The proportion of patients who achieved inactive disease and the mean CHAQ-DI scores were generally similar from baseline up to Week 16 (<

30 kg BW group) or Week 128 (< 30 kg BW group), and the proportion of patients in clinical remission (> 30 kg BW group only) increased through Week 128.

At the CHMP's request, the MAH has provided an overview of the key efficacy (JADAS-71, CHAQ-DI) and safety laboratory results (neutrophil, platelet, ALT, and AST levels) for the <30 kg group split by dose regimen (TCZ SC Q10D or Q2W). Although with regard to efficacy parameters small differences in favour of the Q10D regimen were observed, the CHMP agrees with the MAH that efficacy (JADAS-71, CHAQ-DI) was largely comparable for patients receiving the TCZ SC Q10D or SC Q2W regimens. Due to very small sample sizes (n=8 for Q10D and n=17 for Q2W) the she small differences observed between these two treatment groups should not be over interpreted. Plots of mean neutrophil, platelet, ALT, and AST levels over visits for patients weighing <30 kg split by dose regimen (Q10D, Q2W) showed comparable results for both dose regimens, although there was potentially a trend towards lower neutrophil counts with the Q10D vs. Q2W regimen. The CHMP concluded that these results indicate that the SC Q10D regimen did not confer any additional efficacy benefit to sJIA patients over the proposed SC Q2W regimen, but could potentially have resulted in a worse safety profile in terms of neutropenia. Therefore, the proposed dosing SC Q2W regimen for patients weighing less than 30 kg was considered adequate by the CHMP.

The very low number of patients between the age of 1 to 2 years in the main study hampers the interpretation of the results on the efficacy in the lowest age group. However, all 3 patients responded well to TCZ SC therapy, completed study WA28118 to Week 52, and entered the LTE study WA29231 for continued treatment with TCZ SC. The safety profile for the 3 sJIA patients aged 1-2 years in study WA28118 was also comparable to patients aged > 2 years.

2.4.3. Conclusions on the clinical efficacy

The results of study WA28118 showed that patients with sJIA initiating treatment with TCZ SC experienced in both BW groups (< 30 kg and > 30 kg) improvement in all efficacy parameters measured. The clinical data for the 3 patients in study WA28118 who were between 1-2 years of age at baseline support the use of TCZ SC in children aged > 1 years.

The overall results were consistent with those seen in the TCZ IV Study WA18221.

For the patients switching from commercial TCZ IV to TCZ SC at baseline, efficacy was maintained or continued improving over the entire course of the study in both BW groups.

Furthermore, the efficacy results from the LTE Study WA29231 showed that TCZ SC improved or maintained efficacy in the < 30 kg and the > 30 kg BW group up to Week 16 and Week 128, respectively.

Although limited data is available regarding the Q2W dosing regimen, the CHMP considered that the proposed dosing regimen (QW for patients > 30 kg and Q2W for patients < 30 kg) was adequate. Indeed, the SC Q10D regimen did not confer any additional efficacy benefit to sJIA patients over the proposed SC Q2W regimen, but could potentially have resulted in a worse safety profile in terms of neutropenia.

In conclusion, the efficacy profile of TCZ SC in children aged > 1 years and weighting at least 10 kg is considered favourable by the CHMP.

2.5. Clinical safety

Introduction

The main study contributing to the safety evaluation of TCZ SC in sJIA is the 52-week open-label Phase 1b pharmacokinetics (PK)/pharmacodynamics (PD) and safety Study WA28118. The safety analyses are based on final data from 51 sJIA patients who received TCZ SC for a total duration of 46.7 patient years (PY). The final TCZ SC safety data from Study WA28118 are compared with intravenous (IV) TCZ safety data from a data cut of the pivotal Phase III Study WA18221 (also known as TENDER), which has a comparable exposure duration and was part of the sJIA TCZ IV dossier leading to approval of the IV formulation of TCZ for sJIA patients in 2011.

Supportive data on the long-term safety of TCZ SC in patients with sJIA are provided from 37 sJIA patients in Study WA29231, the ongoing open-label long-term extension (LTE) of Study WA28118. The analyses are based on data collected up to a clinical cut-off date of 11 August 2017, which contribute an additional duration of 50.25 PYs.

For the analyses of injection site reactions (ISRs), which are specific to the SC mode of administration, the ISR data from Study WA28118 are compared with corresponding ISR data from Study WA28117 investigating TCZ SC in paediatric patients with polyarticular juvenile idiopathic arthritis (pJIA) and from the two pivotal Phase III trials with TCZ SC in adult patients with rheumatoid arthritis (RA): Study WA22762 (also known as SUMMACTA) and Study NA25220 (also known as BREVACTA). All ISR analyses are based on data from patients who received TCZ SC via a pre-filled syringe with a needle safety device (PFS + NSD).

Patient exposure

The WA28118 All TCZ SC population provides safety data from 51 sJIA patients who received at least one dose of open-label TCZ SC. The median treatment duration for the WA28118 All TCZ SC population was 1.0 year and was well balanced across the two BW groups.

The LTE data cut of WA18221 All TCZ IV safety population provides safety data from 112 sJIA patients who received at least one dose of TCZ IV. The median treatment duration in the WA18221 LTE All TCZ IV safety population was 1.15 years. The maximum treatment duration in Study WA18221 was 2.0 years.

At the time of the clinical cut-off date (11 August 2017), the WA29231 All TCZ SC LTE safety population comprised 37 patients who received at least one dose of open-label TCZ SC. The median treatment duration in the WA29231 All TCZ SC LTE safety population was 0.77 years. Median treatment duration was longer in the $\geq$ 30 kg BW group (2.30 years) than in the < 30 kg group (0.35 years). The maximum treatment duration in the WA29231 All TCZ SC LTE safety population was 2.9 years.

The total study duration, which is used to calculate rates of AEs per 100 patient years (PY), was 46.74 PY in TCZ SC Study WA28118, 132.40 PY in the LTE data cut of TCZ IV Study WA18221, and 50.25 PY in TCZ SC LTE Study WA29231.

Table 26 Summary of exposure to study drug in studies WA28118 (TCZ SC), WA29231 (TCZ SC LTE), and WA18221 (TCZ IV) in sJIA Patients (Safety Populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112[b]
Study duration (years)[c]									
Mean (SD)	0.92 (0.24)	0.92 (0.28)	0.92 (0.26)	0.82 (0.90)	1.87 (0.90)	1.36 (1.04)	1.14 (0.32)	1.23 (0.32)	1.18 (0.32)
Median	1.00	1.00	1.00	0.35	2.30	0.77	1.09	1.19	1.14
Min-Max	0.0-1.1	0.1-1.0	0.0-1.1	0.0-2.6	0.7-2.9	0.0-2.9	0.4-2.0	0.3-1.9	0.3-2.0
Sum (PY)	22.95	23.79	46.74	14.73	35.52	50.25	57.18	63.81	132.40
Treatment duration (years)[d]									
Mean (SD)	0.90 (0.26)	0.90 (0.28)	0.90 (0.27)	0.80 (0.92)	1.87 (0.90)	1.35 (1.04)	1.14 (0.34)	1.22 (0.34)	1.18 (0.34)
Median	1.00	1.00	1.00	0.34	2.31	0.79	1.11	1.21	1.15
Min-Max	0.0 - 1.0	0.0 - 1.0	0.0 - 1.0	0.0 – 2.6	0.6 – 2.9	0.0 – 2.9	0.16-2.00	0.19-1.88	0.16-2.00

LTE = long-term extension; IV = intravenous; SC = subcutaneous; SD = standard deviation; Q2/3/4W = every 2/3/4 weeks; TCZ = tocilizumab; PY = patient years.

a Data on placebo treatment received in Part I of Study WA18221 are excluded.

b The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

c Duration in study = (date of last assessment - date of first study medication dose +1 day)/365.25. Sum is across all patients in the treatment arm and is used to calculate AE rates per 100 PY.

d Treatment duration (years) = (date of last dose - date of first TCZ dose +15)/365.25.

Adverse events

Table 27 Comparison of AE rates from TCZ SC (WA28118), TCZ IV (WA18221), and LTE TCZ SC (WA29231)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25 No. (%)	162 mg QW (≥ 30 kg) N = 26 No. (%)	All TCZ SC N = 51 No. (%)	162 mg Q10D or Q2W (< 30 kg) N = 18 No. (%)	162 mg QW (≥ 30 kg) N = 19 No. (%)	All TCZ SC LTE N = 37 No. (%)	12 mg/kg Q2W (< 30 kg) N = 50 No. (%)	8 mg/kg Q2W (≥ 30 kg) N = 52 No. (%)	All TCZ IV N = 112[b] No. (%)
Duration in study (PY)	22.95	23.79	46.74	14.73	35.52	50.25	57.18	63.81	132.40
Pts with at least one:									
AE	25 (100.0%)	25 (96.2%)	50 (98.0%)	10 (55.6%)	17 (89.5%)	27 (73.0%)	49 (98.0)	51 (98.1)	110 (98.2)
No. of AEs	233	328	561	83	170	253	559	489	1137
Rate per 100 PY (95% CI)	1015.3 (889.1, 1154.3)	1378.7 (1233.5, 1536.3)	1200.3 (1103.0, 1303.8)	563.5 (448.8, 698.5)	478.6 (409.4, 556.2)	503.5 (443.3, 569.5)	977.7 (898.3, 1062.2)	766.3 (699.9, 837.4)	858.8 (809.6, 910.2)
SAE	5 (20.0%)	2 (7.7%)	7 (13.7%)	1 (5.6%)	1 (5.3%)	2 (5.4%)	14 (28.0%)	9 (17.3%)	25 (22.3%)
No. of SAEs	7	2	9	1	1	2	17	13	33
Rate per 100 PY (95% CI)	30.5 (12.3, 62.8)	8.4 (1.0, 30.4)	19.3 (8.8, 36.6)	6.8 (0.2, 37.8)	2.8 (0.1, 15.7)	4.0 (0.5, 14.4)	29.7 (17.3, 47.6)	20.4 (10.9, 34.8)	24.9 (17.2, 35.0)
AE leading to withdrawal	1 (4.0%)	1 (3.8%)	2 (3.9%)	0	0	0	2 (4.0%)	2 (3.8%)	4 (3.6%)
No. of AEs	3	1	4	0	0	0	2	2	4
Rate per 100 PY (95% CI)	13.1 (2.7, 38.2)	4.2 (0.1, 23.4)	8.6 (2.3, 21.9)	0	0	0	3.5 (0.4, 12.6)	3.1 (0.4, 11.3)	3.0 (0.8, 7.7)
AE leading to dose inter.	7 (28.0%)	6 (23.1%)	13 (25.5%)	3 (16.7%)	4 (21.1%)	7 (18.9%)	24 (48.0)	28 (53.8)	57 (50.9)
No. of AEs	18	10	28	5	10	15	66	79	164
Rate per 100 PY (95% CI)	78.4 (46.5,124.0)	42.0 (20.2, 77.3)	59.9 (39.8, 86.6)	33.9 (11.0, 79.2)	28.2 (13.5, 51.8)	29.9 (16.7, 49.2)	115.4 (89.3, 146.9)	123.8 (98.0, 154.3)	123.9 (105.6, 144.3)

Note: The most directly comparable treatment groups from Study WA28118 and LTE Study WA18221 are highlighted with matching colors.

[a] Data on placebo treatment received in Part I of Study WA18221 are excluded.

[b] The 'All TCZ' group presented for WA18221 has an n = 112 because it includes patients who switched from one of the two TCZ doses during the study; these 'switcher' groups 'TCZ 8 mg/kg to TCZ 12 mg/kg' n = 1 and 'TCZ 12 mg/kg to TCZ 8 mg/kg' n = 9 are not shown.

CI: confidence interval; PY: patient years.

Duration in study for WA28118 and WA29231 = (date of last safety assessment – date of first TCZ dose + 1 day) / 365.25.

Duration in LTE Study WA18221 = (date of last assessment – date of first TCZ dose + 1) / 365.25.

For rates, multiple occurrences of the same event in one individual are counted. MedDRA versions used for analyses: version 20.0 for Study WA28118 and LTE Study WA29231; version 13.0 for Study WA18221.

- **Study WA28118**

Table 28 Overview of key safety results from Study WA28118

	TCZ SC 162 mg Q10D or Q2W (< 30 kg) n = 25	TCZ SC 162 mg QW (≥ 30 kg) n = 26	All TCZ N = 51
Total no. of patients with at least one			
AE	25 (100%)	25 (96.2%)	50 (98.0%)
SAE	5 (20.0%)	2 (7.7%)	7 (13.7%)
AE with fatal outcome	2 (8.0%)	0	2 (3.9%)
AE leading to withdrawal from treatment	1 (4.0%)	1 (3.8%)	2 (3.9%)
AE leading to dose interruption	7 (28.0%)	6 (23.1%)	13 (25.5%)
AESIs			
Serious Infections	4 (16.0%)	0	4 (7.8%)
Injection site reactions	5 (20.0%)	16 (61.5%)	21 (41.2%)
Hypersensitivity Events[a]	2 (8.0%)	1 (3.8%)	3 (5.9%)
Serious Bleeding (SMQ wide)	1 (4.0%)	0	1 (2.0%)
Selected AEs			
Infections and Infestation	22 (88.0%)	18 (69.2%)	40 (78.4%)
Neutropenia	5 (20.0%)	8 (30.8%)	13 (25.5%)
Thrombocytopenia	2 (8.0%)	0	2 (3.9%)
Macrophage Activation Syndrome	0	0	0

[a] Hypersensitivity events were defined as AEs (excluding ISRs) during or within 24 hours of TCZ treatment and not unrelated to study medication.

Investigator text for AEs encoded using MedDRA version 20.0. Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once.

No events were reported for anaphylactic reactions using SMQ Narrow, anaphylactic reactions using Sampson's Criteria, demyelinating AEs (SMQ narrow), gastrointestinal AEs (SMQ Narrow), serious hepatic AEs, malignancies (SMQ narrow), serious myocardial infactions (SMQ narrow), opportunistic infections and serious stroke (ischaemic or hemorrhagic cerebrovascular SMQ narrow).

The majority of sJIA patients (50/51 [98.0%]) in Study WA28118 had at least one AE during treatment; 25/25 (100%) patients in the < 30 kg and 25/26 (96.2%) patients ≥ 30 kg.

The majority of patients (37/51, 72.5%) in the All TCZ group experienced AEs of Grade 1 or Grade 2 maximum intensity. Nine patients (17.6%; 8 < 30 kg and 1 < 30 kg) experienced AEs of Grade 3 maximum intensity (pneumonia, abscess soft tissue, croup infectious, oedema peripheral, cough, neutropenia, contusion, neck pain, juvenile idiopathic arthritis, increased ALT, increased AST, vertigo, and hypersensitivity). One patient (2.0%, ≥ 30 kg) experienced an AE of Grade 4 maximum intensity (abdominal pain). There were two patients with Grade 5 AEs (sepsis and pulmonary haemorrhage), both in the < 30 kg.

The most common SOCs (≥ 15.0% of patients) in which AEs were reported for the All TCZ group were:

- Infections and infestations (78.4%)
- General disorders and administration site conditions (52.9%)
- Respiratory, thoracic and mediastinal disorders (49.0%)
- Gastrointestinal disorders (45.1%)
- Blood and lymphatic system disorders (35.3%)

- Injury, poisoning and procedural complications (29.4%)
- Skin and subcutaneous tissue disorders (29.4%)
- Musculoskeletal and connective tissue disorders (27.5%)
- Investigations (15.7%)

By preferred term, the most commonly reported AEs (≥ 10% of patients) in the All TCZ group, irrespective of treatment relationship, were viral URTI as well as neutropenia (both 25.5%), cough (23.5%), URTI (21.6%), injection site erythema (19.6%), vomiting (17.6%), rash (15.7%), diarrhoea (13.7%), and rhinitis, injection site pain, oropharyngeal pain, abdominal pain, leukopenia, headache, and injection site pruritus (all 11.8%), which were generally consistent with the most commonly reported AEs in the LTE data cut of WA18221.

The overall rate of AEs in the WA28118 All TCZ SC population was 1200.3 [95% CI: 1103.0, 1303.8] AEs per 100 PY based on a total of 561 AEs. This rate appears higher than the rate observed in the WA18221 LTE All TCZ IV population (858.8 [95% CI: 809.6, 910.2] AEs per 100 PY).

Body weight subgroups

Table 29 Primary SOCs with different overall AE rates in patients > 30 kg compared with patients < 30 kg (WA28118)

	All TCZ (N=51)	
System Organ Class	**<30 kg BW Group n=25**	**≥30 kg BW Group n=26**
Higher Rate in < 30 kg BW Group		
Infections and infestations	76 AEs 331.2 (260.9, 414.5)	45 AEs 189.2 (138.0, 253.1)
Investigations	14 AEs 61.0 (33.4, 102.4)	3 AEs 12.6 (2.6, 36.9)
Higher Rate in ≥ 30 kg BW Group		
General disorders and administration site conditions	16 AEs 69.7 (39.8, 113.2)	122 AEs 512.8 (425.9, 612.3)
Nervous systems disorders	No AEs –	16 AEs 67.3 (38.4, 109.2)
Eye disorders	1 AE 4.4 (0.1, 24.3)	9 AEs 37.8 (17.3, 71.8)

AE rates per 100 patient years with 95% confidence intervals are presented.

Analysis of the WA28118 data by body weight group showed a higher AE rate in patients in the ≥ 30 kg compared with patients in the < 30 kg (1378.7 [95% CI: 1233.5, 1536.3] vs. 1015.3 [889.1, 1154.3], respectively).

The higher overall AE rate in patients weighing ≥ 30 kg was primarily driven by higher AE rates in the SOCs General disorders and administration site conditions (mostly injection site papules which was mainly driven by a single patient who reported 39 AEs with this term), Nervous systems disorders (mostly headache), and Eye disorders (with overlapping 95% CIs; mostly iridocyclitis).

Conversely, higher AE rates were observed in patients in the < 30 kg compared with patients in the ≥ 30 kg in the Infections and Infestations (mainly upper respiratory tract infection and viral upper respiratory tract infection) and Investigations (with overlapping 95% CIs; mainly increased ALT and increased AST) SOCs.

Within the < 30 kg, the AE rates were similar between the Q10D dosing group (984.5 [95% CI: 767.5, 1243.9]) and the Q2W dosing group (1029.0 [877.1, 1199.7]). The overall AE rates were similar in TCZ naive and prior TCZ patients (1196.2 [95% CI: 1064.6, 1339.5] vs. 1205.0 [95% CI: 1063.2, 1360.4], respectively).

- **LTE Study WA29231**

At the time of the clinical cut-off for this SCS (11 August 2017), 27/37 (73.0%) sJIA patients in LTE Study WA29231 had experienced a total of 253 AEs; 10/18 (55.6%) patients in the < 30 kg and 17/19 (89.5%) patients in the ≥ 30 kg.

The overall rate of AEs in LTE Study WA29231 was 503.5 [95% CI: 443.3, 569.5] per 100 PY. This is lower than the rate in Study WA28118 (1200.3 [95% CI: 1103.0, 1303.8] AEs per 100 PY), indicating a declining trend in the rate of AEs over time in sJIA patients receiving TCZ SC.

Consistent with Study WA28118, the most common (≥ 15% of patients) SOCs in which AEs were reported were:

- Infections and Infestations (59.5%)
- Gastrointestinal Disorders (27.0%)
- General Disorders and Administration Site Conditions (27.0%)
- Skin and Subcutaneous Tissue Disorders (27.0%)
- Musculoskeletal and Connective Tissue Disorders (24.3%)
- Respiratory, Thoracic and Mediastinal Disorders (18.9%)
- Blood and Lymphatic System Disorders (16.2%)

By preferred term, the most commonly reported AEs (≥ 10% of patients) in the All TCZ group, irrespective of treatment relationship, were URTI and viral URTI (both 21.6%), pyrexia (16.2%), cough, arthralgia, and rash (all 13.5%), and vomiting, ear infection, influenza, and neck pain (all 10.8%).

The overall rate of AEs in LTE Study WA29231 was 503.5 [95% CI: 443.3, 569.5] per 100 PY. This is lower than the rate in Study WA28118 (1200.3 [95% CI: 1103.0, 1303.8] AEs per 100 PY), indicating a declining trend in the rate of AEs over time in sJIA patients receiving TCZ SC.

Body weight subgroups

The overall AE rate was similar in the two BW subgroups of Study WA29231; 563.5 [95% CI: 448.8, 698.5] per 100 PY in the < 30 kg and 478.6 [95% CI: 409.4, 556.2] per 100 PY in the ≥ 30 kg.

SOCs with a notably higher AE rate in patients in the ≥ 30 kg were Gastrointestinal Disorders (mostly odynophagia) and General Disorders and Administration Site Conditions (mostly ISR-related AEs [injection site swelling]), whereas SOCs with a notably higher AE rate in the < 30 kg were Infections and Infestations (mostly URTI).

Serious adverse event/deaths/other significant events

Death

Table 30 Comparison of death rates in TCZ SC Studies WA28118 and WA29231 and TCZ IV Study WA18221 (Safety Populations)

	TCZ SC						TCZ IV					
	Study WA28118 (Week 52)			Cumulative Studies WA28118 and LTE WA29231[a]			Study WA18221 (LTE Cut-off May 2010)[b,c]			Final (260-Week) Study WA18221[b]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC LTE N = 51	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112	12 mg/kg Q2W (< 30 kg) N = 59	8 mg/kg Q2W (≥ 30 kg) N = 53	All TCZ IV N = 112
Study duration (years)[d]	22.95	23.79	46.74	37.68	59.31	96.99	57.18	63.81	132.40	190.87	174.45	365.32
Number of fatal events	2	0	2	2	0	2	0	0	1[e]	3	1	4
AE Rate per 100 PY (95% CI)	8.7 (1.1, 31.5)	–	4.3 (0.5, 15.5)	5.3 (0.6, 19.2)	–	2.1 (0.2, 7.4)	–	–	0.8 (0.0, 4.2)	1.6 (0.3, 4.6)	0.6 (0.0, 3.2)	1.1 (0.3, 2.8)

LTE = long-term extension; IV = intravenous; SC = subcutaneous; Q10D = every 10 days; QW = every week; Q2W = every 2 weeks; PY = patient years; TCZ = tocilizumab.

[a] No deaths were reported up to the clinical cut-off date of TCZ SC LTE Study WA29231.

[b] Data on placebo treatment received in Part I of Study WA18221 are excluded.

[c] The 'All TCZ' group presented for WA18221 has an n = 112 because it includes patients who switched from one of the two TCZ doses during the study; these 'switcher' groups 'TCZ 8 mg/kg to TCZ 12 mg/kg' n = 1 and 'TCZ 12 mg/kg to TCZ 8 mg/kg' n = 9 are not shown.

[d] Duration in study for WA28118 and WA29231 = (date of last safety assessment – date of first TCZ dose + 1 day) / 365.25; duration in study for WA18221 LTE = (date of last assessment – date of first TCZ dose + 1) / 365.25; duration in study for 260-Week WA18221 = (date of last assessment relating to Q2W dosing - date of first TCZ dose + 1) / 365.25.

[e] The patient who died in the LTE datcut (May 2010) of WA18221 was in the 'TCZ 12 mg/kg to TCZ 8 mg/kg' switcher group.

- **Study WA28118**

In study WA28118 two patients, both weighing < 30 kg at baseline and both receiving concomitant steroids, died during the study. Both AEs leading to death were considered related to study treatment. One TCZ naive patient had a fatal AE of pulmonary haemorrhage on Day 15 after presenting with pneumonia; the patient received one dose of TCZ SC. One patient died from sepsis (serious infection) on Day 262 after having received 20 doses of TCZ SC. At the time of death, this patient weighed > 30 kg and was receiving TCZ QW.

- **LTE Study WA29231**

No deaths were reported up to the clinical cut-off date of TCZ SC LTE Study WA29231.

- **Final CSR WA18221**

In the entire TCZ IV Study WA18221, there were a total of 4 deaths (260-Week WA18221 CSR). Three of these deaths were considered unrelated to study treatment; one death was considered possibly related to study treatment.

Serious adverse event/other significant events

- **Study WA28118**

A total of 9 SAEs were reported by 7 patients (13.7%), resulting in an SAE rate of 19.3 events per 100 PY (95% CI: 8.8, 36.6). This is consistent with incidence and rate of SAEs observed in the All TCZ IV LTE population of Study WA18221 (22.3% and 24.9 [95%CI: 17.2, 35.0] SAEs per 100 PY). A higher proportion of patients in the < 30 kg experienced an SAE in both the TCZ SC WA28118 and TCZ IV WA18221 studies compared with patients in the ≥ 30 kg. In Study WA28118, the majority of the SAEs (5/9) were in the Infections and Infestations SOC (pneumonia [2 events], abscess soft tissue, oral

candidiasis, and sepsis), which were reported in 4 patients in the < 30 kg. The most commonly reported SAEs in the All TCZ IV LTE population of Study WA18221 were also in the Infections and Infestations SOC.

Table 31 Serious adverse events by SOC, preferred term and NCI CTCAE Grade

MedDRA System Organ Class MedDRA Preferred Term	TCZ SC 162 mg Q10D or Q2W (< 30 kg) (N=25)	TCZ SC 162 mg QW (>= 30 kg) (N=26)	All TCZ (N=51)
Total number of patients with at least one adverse event	5 (20.0%)	2 (7.7%)	7 (13.7%)
Overall total number of events	7	2	9
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	4 (16.0%)	0	4 (7.8%)
Total number of events	5	0	5
PNEUMONIA	2 (8.0%)	0	2 (3.9%)
ABSCESS SOFT TISSUE	1 (4.0%)	0	1 (2.0%)
ORAL CANDIDIASIS	1 (4.0%)	0	1 (2.0%)
SEPSIS	1 (4.0%)	0	1 (2.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total number of patients with at least one adverse event	1 (4.0%)	1 (3.8%)	2 (3.9%)
Total number of events	1	1	2
JUVENILE IDIOPATHIC ARTHRITIS	1 (4.0%)	1 (3.8%)	2 (3.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one adverse event	1 (4.0%)	0	1 (2.0%)
Total number of events	1	0	1
PULMONARY HAEMORRHAGE	1 (4.0%)	0	1 (2.0%)
EAR AND LABYRINTH DISORDERS			
Total number of patients with at least one adverse event	0	1 (3.8%)	1 (2.0%)
Total number of events	0	1	1
VERTIGO	0	1 (3.8%)	1 (2.0%)

Investigator text for AEs encoded using MedDRA version 20.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

In the < 30 kg, 5 patients experienced 7 SAEs, 4 of which were considered related to study drug by the investigator.

In the ≥ 30 kg, 2 patients experienced 2 SAEs, one of which was considered related to study treatment by the investigator

LTE Study WA29231

In the TCZ SC LTE Study WA29231, 2/37 (5.4%) patients experienced a total of 2 SAEs up to the clinical cut-off. One SAE was reported in the < 30 kg BW; one SAE was reported in the ≥ 30 kg BW.

Adverse events of special interest

Table 32 Incidence of AESIs and selected AEs in sJIA patients treated with SC (Studies WA28118 and WA29231) or IV (Study WA18221 LTE) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25 No. (%)	162 mg QW (≥ 30 kg) N = 26 No. (%)	All TCZ SC N = 51 No. (%)	162 mg Q10D or Q2W (< 30 kg) N = 18 No. (%)	162 mg QW (≥ 30 kg) N = 19 No. (%)	All TCZ SC LTE N = 37 No. (%)	12 mg/kg Q2W (< 30 kg) N = 50 No. (%)	8 mg/kg Q2W (≥ 30 kg) N = 52 No. (%)	All TCZ IV N = 112[b] No. (%)
AESI									
Serious infections	4 (16.0%)	0	4 (7.8%)	1 (5.6%)	0	1 (2.7%)	9 (18.0%)	5 (9.6%)	15 (13.4%)
Opportunistic infections	0	0	0	0	0	0	NA[e]	NA[e]	NA[e]
Hypersensitivity reactions[c]	2 (8.0%)	1 (3.8%)	3 (5.9%)	0	0	0	14 (28.0%)	10 (19.2%)	25 (22.3%)
Anaphylactic reactions									
Sampson's Criteria	0	0	0	0	0	0	1 (2.0%)	1 (1.9%)	2 (1.8%)
SMQ Narrow	0	0	0	0	0	0	0	0	0
Injection site reactions	5 (20.0%)	16 (61.5%)	21 (41.2%)	0	3 (15.8%)	3 (8.1%)	NA	NA	NA
Serious bleeding AEs	1 (4.0%)	0	1 (2.0%)	0	0	0	0	0	0
Other AESIs[d]	0	0	0	0	0	0	0	0	0
Selected AEs									
Infection AE	22 (88.0%)	18 (69.2%)	40 (78.4%)	9 (50.0%)	13 (68.4%)	22 (59.5%)	43 (86.0%)	44 (84.6%)	97 (86.6%)
Neutropenia AEs	5 (20.0%)	8 (30.8%)	13 (25.5%)	2 (11.1%)	3 (15.8%)	5 (13.5%)	11 (22.0%)	8 (15.4%)	20 (17.9%)
Thrombocytopenia AEs	2 (8.0%)	0	2 (3.9%)	0	1 (5.3%)	1 (2.7%)	2 (4.0%)	2 (3.8%)	4 (3.6%)
MAS	0	0	0	0	0	0	1 (2.0%)	1 (1.9%)	3 (2.7%)

AESI = adverse event of special interest; IV = intravenous; LTE = long-term extension; NA = not available; Q10D = every 10 days; QW = every week; Q2W = every 2 weeks; SC = subcutaneous; SMQ = standard MedDRA query ; TCZ = tocilizumab; MAS = macrophage activation syndrome (preferred term of histiocytosis haematophagic); NA = not applicable.

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.

[a] Data on placebo treatment received in Part I of study WA18221 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

[c] AEs [excluding ISRs] during or within 24 hours of TCZ treatment (injection or infusion) and not unrelated to study medication.

[d] Other AESIs are serious hepatic events, serious stroke events, serious myocardial infarction events, gastrointestinal perforations, demyelinating disorders, and malignancies.

[e] MedDRA basket for Opportunistic Infections not available for MedDRA Version 13.

Infections

Overall, 40/51 (78.4%) patients in the WA28118 All TCZ SC safety population reported at least one infection AE. The most frequent infection AEs (occurring in > 10% of patients) in the WA28118 All TCZ SC safety population were viral upper respiratory tract infection (25.5%), upper respiratory tract infection (21.6%), rhinitis (11.8%), and gastroenteritis (9.8%).The majority of infection events were Grade 1 or Grade 2.

Table 33 Rate of infections in sJIA patients treated with SC (Studies WA28118 and WA29231) or IV (Study WA18221) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112[b]
Duration in study (PY)	22.95	23.79	46.74	14.73	35.52	50.25	57.18	63.81	132.40
Infection AE									
No. pts (%)	22 (88.0%)	18 (69.2%)	40 (78.4%)	9 (50.0%)	13 (68.4%)	22 (59.5%)	43 (86.0%)	44 (84.6%)	97 (86.6%)
Total no. AEs	76	45	121	38	51	89	214	128	371
Rate per 100 PY [95% CI]	331.2 [260.9, 414.5]	189.2 [138.0, 253.1]	258.9 [214.8, 309.3]	258.0 [182.6,354.1]	143.6 [106.9,188.8]	177.1 [142.2,218.0]	374.3 [325.8, 427.9]	200.6 [167.4, 238.5]	280.2 [252.4, 310.2]
Serious infections									
No. pts (%)	4 (16.0%)	0	4 (7.8%)	1 (5.6%)	0	1 (2.7%)	9 (18.0%)	5 (9.6%)	15 (13.4%)
Total no. AEs	5	0	5	1	0	1	9	5	15
Rate per 100 PY [95% CI]	21.8 [7.1, 50.8]	-	10.7 [3.5, 25.0]	6.8 [0.2, 37.8]	-	2.0 [0.1, 11.1]	15.7 [7.2, 29.9]	7.8 [2.5, 18.3]	11.3 [6.3, 18.7]
Opportunistic infections									
No. pts (%)	0	0	0	0	0	0	NA[c]	NA[c]	NA[c]

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.

AESI = adverse event of special interest; IV = intravenous; LTE = long-term extension; NA = not applicable; Q10D = every 10 days; QW = every week; Q2W = every 2 weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] Data on placebo treatment received in Part I of study WA18221 are excluded. [b] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown. [c] MedDRA basket for Opportunistic Infections not available for MedDRA Version 13.

- **Study WA28118**

The rate of infection AEs in the WA28118 All TCZ SC safety population (258.9 [95% CI: 214.8, 309.3] AEs per 100 PY) was comparable with that in the WA18221 LTE All TCZ IV safety population (280.2 [95% CI: 252.4, 310.2] AEs per 100 PY), indicating no increase in rate of infection with the SC regimen compared with the IV regimen.

Analysis of the WA28118 TCZ SC data by TCZ status (TCZ naive vs. prior TCZ) showed that the rate was lower in the TCZ naive group (219.3 [95% CI: 165.2, 285.5] vs. 304.7 [95% CI: 235.7, 387.7] AEs per 100 PY, respectively).

The rate of serious infections in the WA28118 All TCZ SC safety population (10.7 [95% CI: 3.5, 25.0]) is comparable with the rate observed in the WA18221 LTE All TCZ IV safety population (11.3 [95% CI: 6.34, 18.69]), indicating no increase in the rate of serious infection with the SC regimen compared with the IV regimen.

By BW, the rate of serious infections in the < 30 kg of TCZ SC Study WA28118 was 21.8 (95% CI: 7.1, 50.8), whereas no patients ≥ 30 kg experienced a serious infection; a (numerically) higher rate of serious infections in the < 30 kg was also observed in the LTE data cut of TCZ IV Study WA18221 (15.7 [95%CI: 7.20, 29.88] vs. 7.8 [95%CI: 2.54, 18.29]).

- **LTE Study WA29231**

Overall, 22/37 (59.5%) patients in the WA29231 LTE All TCZ SC safety population reported a total of 89 infection AEs up to the clinical cut-off date. The most frequent individual infection AEs in the WA29231 LTE All TCZ SC safety population (occurring in > 10% of patients) were URTI (8/37 [21.6%]), viral URTI (8/37 [21.6%]), ear infection (4/37 [10.8%]), and influenza (4/37 [10.8%]).

The rate of all infection AEs in the WA29231 LTE All TCZ SC population was 177.1 (95% CI: 142.2, 218.0) AEs per 100 PY. This is numerically lower than the rate in the WA28118 All TCZ SC population

(258.9 [95% CI: 214.8, 309.3] AEs per 100 PY; Table 19), indicating no increase in the rate of infection AEs over time in sJIA patients treated with TCZ SC.

In both TCZ SC Studies WA28118 and WA29231, the rate of infection AEs was higher in the < 30 kg (331.2 AEs per 100 PY [CI: 260.9, 414.5] in WA28118 and 258.0 AEs per 100 PY [CI: 182.6, 354.1] in WA29231) than in the > 30 kg (189.2 AEs per 100 PY [CI: 138.0, 253.1] in WA28118 and 143.6 AEs per 100 PY [CI: 106.9, 188.8] in WA29231).

Serious infections

- **Study WA28118**

Of the 121 infection AEs reported during TCZ SC Study WA28118 5 infections in 4 patients < 30 kg were reported as SAEs (1 on Q10D dosing, 2 on Q2W dosing and 1 on QW dosing [patient's BW increased to ≥ 30 kg during the study] at the time of the serious infection). There were no serious infections in the ≥ 30 kg.

The 5 serious infections were pneumonia (2 events), abscess soft tissue, oral candidiasis, and sepsis. One of the pneumonia SAEs and the abscess soft tissue SAE resolved, while the other pneumonia SAE and the oral candidiasis SAE did not resolve. The SAE of sepsis led to death (see above).

Body weight subgroups

The rate of serious infection in the < 30 kg subgroup of TCZ SC Study WA28118 was 21.8 [95% CI: 7.1, 50.8] events per 100 PY, whereas no patients ≥ 30 kg experienced a serious infection.

- **LTE Study WA29231**

One patient experienced a serious infection in LTE study WA29231 up to the clinical cut-off date. The patient was in the < 30 kg subgroup and experienced pneumonia mycoplasmal (Grade 3) with onset on Day 108. The event resolved.

Opportunistic infections

No opportunistic infections were reported in TCZ SC Studies WA28118 or WA29231.

Hypersensitivity reactions

Table 34 Rate of hypersensitivity reactions in sJIA Patients treated with SC (Studies WA28118 and WA29231) or IV (Study WA18221) TCZ (Safety Populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112[b]
Duration in study (PY)	22.95	23.79	46.74	14.73	35.52	50.25	57.18	63.81	132.40
Hypersensitivity reactions									
No. pts (%)	2 (8.0%)	1 (3.8%)	3 (5.9%)	0	0	0	14 (28.0%)	10 (19.2%)	25 (22.3%)
Total no. AEs	3	1	4	0	0	0	23	16	40
Rate per 100 PY (95% CI)	13.1 [2.7, 38.2]	4.2 [0.1, 23.4]	8.6 [2.3, 21.9]	-	-	-	40.2 [25.5, 60.4]	25.1 [14.3, 40.7]	30.2 [21.6, 41.1]

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.
IV = intravenous; LTE = long-term extension; PY = patient years; Q10D = every 10 days; QW = every week; Q2W = every 2 weeks; SC = subcutaneous; TCZ = tocilizumab.
[a] Data on placebo treatment received in Part I of study WA18221 are excluded.
[b] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

- **Study WA28118**

Overall, 3/51(5.9%) patients in the WA28118 All TCZ SC population experienced a total of 4 potential hypersensitivity reaction AEs; hypersensitivity (preferred term), platelet count decreased, pruritus, and pyrexia. All events were non-serious, Grade 1 or 2, and did not lead to withdrawal.

Note that a Grade 3 hypersensitivity AE (preferred term) in one patient was not counted as a hypersensitivity reaction as defined above since it was recorded as an ISR. However, in addition to swelling and warmth at the injection site, the patient showed systemic symptoms of headache (Grade 3), vertigo, and fatigue (both Grade 1).

Body weight subgroups

Of the 4 potential hypersensitivity reaction AEs reported during study WA28118, 3 events occurred in the < 30 kg and 1 event occurred in the > 30 kg subgroup.

- **LTE Study WA29231**

No potential hypersensitivity reaction AEs were identified.

Injection site reactions

Table 35 Rate of injection site reactions in sJIA (Studies WA28118 and WA29231) and pJIA (Study WA28117) (Safety Populations)

	sJIA						pJIA		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA28117 (Week 52)		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	162 mg Q3W (< 30 kg) N = 27	162 mg Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52
Duration in study (PY)	22.95	23.79	46.74	14.73	35.52	50.25	26.60	23.83	50.43
No. pts (%)	5 (20.0%)	16 (61.5%)	21 (41.2%)	0	3 (15.8%)	3 (8.1%)	4 (14.8%)	11 (44.0%)	15 (28.8%)
ISRs [a]									
Total no. AEs	14	122	136	0	18	18	10	47	57
Rate per 100 PY [95% CI]	61.0 [33.4,102.4]	512.8 [425.9,612.3]	291.0 [244.1,344.2]	-	50.7 [30.0, 80.1]	35.8 [21.2, 56.6]	37.6 [18.03,69.14]	197.2 [144.92, 262.27]	113.0 [85.61,146.44]

Note: The most directly comparable treatment groups from Study WA28118 and Study WA28117 are highlighted with matching colors.

IV = intravenous; LTE = long-term extension; PY = patient years; Q10D = every 10 days; QW = every week; Q2W = every 2 weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] All individual ISR symptoms are counted.

ISR AEs occurred at the site of TCZ SC injection (ISRs) in 21/51 (41.2%) patients in Study WA28118 and in 3/37 (8.1%) sJIA patients in LTE Study WA29231. The overall rate of ISRs in sJIA patients was 291.0 [95% CI: 244.1, 344.2].

With the exception of one non-serious Grade 3 event (see above hypersensitivity event) in Study WA28118, all ISR events were non-serious Grade 1 or 2 events, and none required patient withdrawal from treatment or dose interruption.

In Study WA28118, ISRs following TCZ SC administration were more common in sJIA patients weighing ≥ 30 kg (61.5%) at baseline than in patients <30 kg (20.0%). The higher rate in the ≥ 30 kg subgroup was mainly driven by four female patients who reported 90 of the 122 (73.8%) ISRs reported in that group.

Serious bleeding events

One patient in the < 30 kg BW group of Study WA28118 had a serious bleeding AE (pulmonary haemorrhage) that was fatal.

No serious bleeding events were reported in LTE Study WA29231.

Neutropenia adverse events

Table 36 Rate of neutropenia AEs in sJIA patients treated with SC (Studies WA28118 and WA29231) or IV (Study WA18221) TCZ (Safety Populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112[b]
Duration in study (PY)	22.95	23.79	46.74	14.73	35.52	50.25	57.18	63.81	132.40
No. pts (%)	5 (20.0%)	8 (30.8%)	13 (25.5%)	2 (11.1%)	3 (15.8%)	5 (13.5%)	11 (22.0%)	8 (15.4%)	20 (17.9%)
Total no. AEs	21	12	33	3	3	6	27	21	58
Rate per 100 PY (95% CI)	91.5 [56.6, 139.9]	50.4 [26.1, 88.1]	70.6 [48.6, 99.2]	20.4 [4.2, 59.5]	8.4 [1.7, 24.7]	11.9 [4.4, 26.0]	47.2 [31.1, 68.7]	32.9 [20.4, 50.3]	43.8 [33.3, 56.6]

IV = intravenous; LTE = long-term extension; PY = patient years; Q10D = every 10 days; QW = every week; Q2W = every 2 weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] Data on placebo treatment received in Part I of study WA18221 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

- **Study WA28118**

In Study WA28118, 13/51 (25.5%) sJIA patients experienced a total of 33 neutropenia AEs after receiving TCZ SC; 5/25 (20.0%) patients in the <30 kg and 8/26 (30.8%) patients in the > 30 kg. Six of the 13 patients were naive to TCZ and 7 patients had prior TCZ experience. Two of the 13 patients who experienced a neutropenia AE had low neutrophil counts at baseline.

All neutropenia AEs except one were deemed related to study treatment, but none were reported as serious. Seven of the 13 patients had dose interruptions as a result of their neutropenia AE.

There were no events of serious infections within 15 days, preceding or following, a neutropenia AE.

- **LTE Study WA29231**

In Study WA29231, 5/37 (13.5%) sJIA patients experienced a total of 6 neutropenia AEs. All 5 patients had previously had a neutropenia event in Study WA28118. All neutropenia events in WA29231 except one were deemed related to study treatment, but none were reported as serious.

There were no events of serious infections within 15 days, preceding or following, a neutropenia event.

Thrombocytopenia adverse events

Thrombocytopenia AEs were reported by 2/51 (3.9%) sJIA patients in Study WA28118 and by 1/37 (2.7%) patients in Study WA29231 following TCZ SC treatment.

There were no serious bleeding events within 15 days, preceding or following, a thrombocytopenia AE in TCZ Studies WA28118 and WA29231.

Other AESIs/Selected AEs

No events were identified in the sJIA TCZ SC studies for opportunistic infections, serious hepatic events, gastrointestinal perforations, demyelinating disorders, serious myocardial infarction events, anaphylactic reactions (SMQ narrow or Sampson's criteria - Sampson et al., 2006), malignancies, or MAS.

Laboratory findings

Neutrophil counts

Table 37 Low neutrophil counts - Summary of worst NCI CTCAE grade post baseline in sJIA patients treated with SC (Studies WA28118 and WA29231) or IV (WA18221 LTE) TCZ (Safety Populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010) [a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112 [b]
n	25	26	51	17	19	36	50	52	112
Neutrophil Counts									
Normal	13 (52.0%)	10 (38.5%)	23 (45.1%)	11 (64.7%)	8 (42.1%)	19 (52.8%)	23 (46.0%)	31 (59.6%)	59 (52.7%)
Grade 1	0 (0.0%)	3 (11.5%)	3 (5.9%)	0 (0.0%)	4 (21.1%)	4 (11.1%)	0 (0%)	5 (9.6%)	5 (4.5%)
Grade 2	8 (32.0%)	5 (19.2%)	13 (25.5%)	2 (11.8%)	4 (21.1%)	6 (16.7%)	18 (36.0%)	11 (21.2%)	31 (27.7%)
Grade 3	4 (16.0%)	8 (30.8%)	12 (23.5%)	2 (11.8%)	3 (15.8%)	5 (13.9%)	7 (14.0%)	5 (9.6%)	15 (13.4%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.0%)	0 (0.0%)	2 (1.8%)
Grade ≥ 3	4 (16.0%)	8 (30.8%)	12 (23.5%)	2 (11.8%)	3 (15.8%)	5 (13.9%)	9 (18.0%)	5 (9.6%)	17 (15.2%)

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.

LTE = long-term extension; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q10D = every 10 days; QW = every week; Q2 = every 2 weeks.

Percentages are based on n (number of valid values).

[a] Data on placebo treatment received in Part I of study WA18221 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

NCI CTCAE grading: Version 4.0 was used in studies WA28118 and WA29231; Version 3.0 was used in study WA18221.

The overall incidence of NCI-CTCAE Grade > 3 post-baseline low neutrophil counts was 23.5% in TCZ SC Study WA28118 compared with 15.2% in the LTE data cut of TCZ IV Study WA18221.

The incidence of Grade > 3 post-baseline low neutrophil counts was higher in patients < 30 kg compared with patients < 30 kg in the TCZ SC Study WA28118 (30.8% vs. 16.0%), which is the opposite of what was observed in the LTE data cut of TCZ IV Study WA18221(> 30 kg: 9.6% vs. < 30 kg: 18.0%). The majority of the Grade 3 decreases in neutrophil counts in patients treated with TCZ SC in the > 30 kg were single occurrences, while all of the Grade 3 decreases in neutrophil counts in the < 30 kg were non-consecutive occurrences in WA28118. Patients who experienced Grade 3 low neutrophil count abnormalities in TCZ SC Study WA28118 generally had lower baseline neutrophil counts compared with patients who did not experience Grade 3 low neutrophil count abnormalities.

There were no Grade 4 low neutrophil counts in either of the TCZ SC Studies (WA28118 and LTE WA29231), while there were two patients with Grade 4 low neutrophil counts in the LTE data cut of Study WA18221.

With the exception of one patient who experienced a serious infection of soft tissue abscess within 15 days of a Grade 2 low neutrophil count, all other serious infection AEs were not within 15 days (preceding or following) a low neutrophil count.

Platelet count

Table 38 Low platelet counts - summary of Worst NCI CTCAE grade post-baseline in sJIA patients treated with SC (Studies WA28118 and WA29231) or IV (WA18221 LTE) TCZ (Safety Populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010) [b]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112 [c]
n	25	26	51	18 [a]	19	37	50	52	112
Normal	15 (60.0%)	24 (92.3%)	39 (76.5%)	11 (61.1%)	15 (78.9%)	26 (70.3%)	33 (66.0%)	44 (84.6%)	86 (76.8%)
Grade 1	10 (40.0%)	2 (7.7%)	12 (23.5%)	4 (22.2%)	3 (15.8%)	7 (18.9%)	17 (34.0%)	7 (13.5%)	25 (22.3%)
Grade 2	0	0	0	0	0	0	0	0	0 (0.0%)
Grade 3	0	0	0	0	0	0	0	1 (1.9%)	1 (0.9%)
Grade 4	0	0	0	0	0[d]	0	0	0	0
Grade ≥ 3	0	0	0	0	0	0	0	1 (1.9%)	1 (0.9%)

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.

LTE = long-term extension; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q10D=every 10 days; QW=every week; Q2= every 2 weeks.

Percentages are based on n (number of valid values).

[a] 3 patients in the ≤ 30 kg BW group had missing post-baseline platelet count assessments.

[b] Data on placebo treatment received in Part I of study WA18221 are excluded.

[c] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

Most sJIA patients in Study WA28118 (76.5%) and LTE Study WA29231 (70.3%) maintained a platelet count within the normal range throughout treatment with TCZ SC. All low platelet count abnormalities in TCZ SC Studies WA28118 and WA29231 were Grade 1.

There were no serious bleeding events within 15 days (preceding or following) a low platelet count in either Study WA28118 or WA29231.

Liver enzymes

Table 39 Liver function profile - summary of highest NCI CTCAE grade post-baseline in sJIA patients treated with SC (Studies WA28118 and WA29231) or IV (WA18221 LTE) TCZ (Safety Populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N=50	8 mg/kg Q2W (≥ 30 kg) N=52	All TCZ IV N=112[b]
n	25	26	51	18[d]	19	37	50	52	112
ALT									
Normal	16 (64.0%)	18 (69.2%)	34 (66.7%)	14 (77.8%)	17 (89.5%)	31 (83.8%)	29 (58.0%)	24 (46.2%)	58 (51.8%)
Grade 1	6 (24.0%)	6 (23.1%)	12 (23.5%)	1 (5.6%)	1 (5.3%)	2 (5.4%)	18 (36.0%)	13 (25.0%)	36 (32.1%)
Grade 2	1 (4.0%)	2 (7.7%)	3 (5.9%)	0	1 (5.3%)	1 (2.7%)	2 (4.0%)	8 (15.4%)	10 (8.9%)
Grade 3	1 (4.0%)	0	1 (2.0%)	0	0	0	1 (2.0%)	7 (13.5%)	8 (7.1%)
Grade 4	1 (4.0%)	0	1 (2.0%)	0	0	0	0	0	0
Grade ≥ 2[c]	3 (12.0%)	2 (7.7%)	5 (9.8%)	0	1 (5.3%)	1 (2.7%)	3 (6.0%)	15 (28.8%)	18 (16.1%)
AST				17[e]	19	36			
Normal	20 (80.0%)	19 (73.1%)	39 (76.5%)	14 (82.4%)	17 (89.5%)	31 (86.1%)	35 (70.0%)	24 (46.2%)	67 (59.8%)
Grade 1	3 (12.0%)	7 (26.9%)	10 (19.6%)	1 (5.9%)	2 (10.5%)	3 (8.3%)	13 (26.0%)	24 (46.2%)	39 (34.8%)
Grade 2	1 (4.0%)	0	1 (2.0%)	0	0	0	1 (2.0%)	3 (5.8%)	4 (3.6%)
Grade 3	1 (4.0%)	0	1 (2.0%)	0	0	0	1 (2.0%)	0	1 (0.9%)
Grade 4	0	0	0	0	0	0	0	1 (1.9%)	1 (0.9%)
Grade ≥ 2[c]	2 (8.0%)	0	2 (3.9%)	0	0	0	2 (4.0%)	4 (7.7%)	6 (5.4%)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	162 mg Q10D or Q2W (< 30 kg) N = 25	162 mg QW (≥ 30 kg) N = 26	All TCZ SC N = 51	162 mg Q10D or Q2W (< 30 kg) N = 18	162 mg QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N=50	8 mg/kg Q2W (≥ 30 kg) N=52	All TCZ IV N=112[b]
n	25	26	51	18[d]	19	37	50	52	112
Total bilirubin									
Normal	24 (96.0%)	20 (76.9%)	44 (86.3%)	14 (77.8%)	16 (84.2%)	30 (81.1%)	47 (94.0%)	40 (76.9%)	96 (85.7%)
Grade 1	1 (4.0%)	3 (11.5%)	4 (7.8%)	0	2 (10.5%)	2 (5.4%)	3 (6.0%)	7 (13.5%)	11 (9.8%)
Grade 2	0	3 (11.5%)	3 (5.9%)	1 (5.6%)	1 (5.3%)	2 (5.4%)	0	5 (9.6%)	5 (4.5%)
Grade 3	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0
Grade ≥ 2	0	3 (11.5%)	3 (5.9%)	1 (5.6%)	1 (5.3%)	2 (5.4%)	0	5 (9.6%)	5 (4.5%)

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.

LTE = long-term extension; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q10D = every 10 days; QW = every week; Q2 = every 2 weeks.

Percentages are based on n (number of valid values).

[a] Data on placebo treatment received in Part I of study WA18221 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

[c] For ALT and AST, a Grade ≥ 2 elevation is a value > 3x ULN in Studies WA28118 and WA29231 (CTCAE version 4.0) and > 2.5x ULN in Study WA18221 (CTCAE version 3.0). See Table 5.

[d] In LTE WA29231, 3 patients in the ≤ 30 kg BW group had missing post-baseline assessments.

[e] In LTE WA29231, 2 patients in the ≤ 30 kg BW group had missing post-baseline assessments.

NCI CTCAE grading: Version 4.0 was used in studies WA28118 and WA29231; Version 3.0 was used in study WA18221.

No patients met the laboratory criteria for Hy's Law in TCZ SC Studies WA28118 or WA29231, and there were no serious hepatic events.

In both studies, the majority of patients had ALT, AST, and bilirubin values within the normal range throughout TCZ SC treatment. The incidence of Grade $\geq$ 2 LFT elevations was comparable between TCZ SC Study WA28118 and the LTE data cut of TCZ IV Study WA18221. The incidence of Grade > 2 LFT elevations reported to up to the clinical cut-off in TCZ SC LTE Study WA29231 generally decreased compared with the core study.

Thirty-nine patients (76.5%) had normal total bilirubin concentrations at baseline; 1 patient had a Grade 2 bilirubin elevation and 11 patients had missing values at baseline.

Post-baseline, 44 (86.3%) patients had normal total bilirubin values throughout TCZ SC treatment, while Grade 1 elevations were seen in 4/39 patients (7.8%) and Grade 2 in 3 patients (5.9%). There were no Grade 3 or 4 elevations in bilirubin.

Lipid parameters

Table 40 Total and LDL cholesterol - Summary of post-baseline elevations in sJIA patients treated with SC (WA28118 and WA29231) or IV (WA18221 LTE) TCZ (Safety Populations)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Cut-off August 2017)			Study WA18221 (LTE Cut-off May 2010)[a]		
	TCZ SC Q10D or Q2W (< 30 kg) N = 25	TCZ SC QW (≥ 30 kg) N = 26	All TCZ SC N = 51	TCZ SC Q10D or Q2W (< 30 kg) N = 18	TCZ SC QW (≥ 30 kg) N = 19	All TCZ SC LTE N = 37	12 mg/kg Q2W (< 30 kg) N = 50	8 mg/kg Q2W (≥ 30 kg) N = 52	All TCZ IV N = 112[b]
Total ≥ 200 mg/dL, n	22	26	48	8	17	25	47	51	107
	6 (27.3%)	11 (42.3%)	17 (35.4%)	3 (37.5%)	4 (23.5%)	7 (28.0%)	14 (29.8%)	15 (29.4%)	33 (30.8%)
LDL ≥ 130 mg/dL, n	22	26	48	8	17	25	43	47	96
	5 (22.7%)	7 (26.9%)	12 (25.0%)	2 (25.0%)	3 (17.6%)	5 (20.0%)	7 (16.3%)	8 (17.0%)	16 (16.7%)

Note: The most directly comparable treatment groups from Study WA28118 and Study WA18221 are highlighted with matching colors.
LTE = long-term extension; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q10D=every 10 days; QW=every week; Q2= every 2 weeks.
Table includes patients with an elevation at baseline. Percentages are based on n (number of patients with at least one post-baseline value).
Patients were fasted for a minimum of 8 hours before sampling.
[a] Data on placebo treatment received in Part I of study WA18221 are excluded.
[b] The 'All TCZ IV' group includes all patients in the WA18221 safety population including those in dose groups not shown.

The majority of sJIA patients had total and LDL cholesterol levels below the elevated concentration cut points of ≥ 200 mg/dL for total cholesterol (fasted) and > 130 mg/dL for LDL-cholesterol (fasted) throughout treatment with TCZ SC (WA28118: 64.6% and 75.0%, respectively; LTE WA29231: 72.0% and 80.0%, respectively).

A comparable proportion of All TCZ sJIA patients in WA28118 and the LTE data cut of WA18221 had post-baseline elevations in total cholesterol (≥ 200 mg/dL) (35.4% vs. 30.8%), whereas a higher proportion of All TCZ sJIA patients in WA28118 had post-baseline elevations in LDL cholesterol (≥ 130 mg/dL) compared to the All TCZ IV sJIA patients in WA18221 LTE (25.0% vs. 16.7%, respectively).

In Study WA28118, the majority of the patients with a post-baseline elevation in total cholesterol had the elevation more than once, whereas the majority of patients with elevations in LDL (≥ 130 mg/dL) cholesterol had single time point occurrences.

In LTE Study WA29231, post-baseline elevations in total (≥ 200 mg/dL) and LDL (≥ 130 mg/dL) cholesterol occurred in 28.0% and 20.0% of the sJIA patients, both of which are slightly lower than the core study; the majority of patients with elevated total or LDL cholesterol had single time point occurrences.

Safety in special populations

Three patients were under the age of 2 years at baseline in Study WA28118:

- A patient aged 17 months with a BW of 10.3 kg on Q10D regimen.
- A patient aged 19 months with a BW of 11.0 kg on Q2W regimen.

- A patient aged 22 months with a BW of 11.5 kg on Q2W regimen.

The lowest BW patient in WA28118 was a girl aged 25 months weighing 9.2 kg at baseline.

Table 41 Safety overview of sJIA Patients < 2 years and the lightest sJIA Patient in WA28118

Patient Number Country (Number of AEs)	Age and Sex	BW	TCZ Status	TCZ SC Dose	SAE(s)	Grade 3 AEs or Grade 3 Laboratory Abnormalities (neutrophils, platelets, LFTs)
< 2 years old						
[redacted] Germany (22 AEs total)	17 months, male	10.3 kg	prior TCZ	Q10D	Abscess soft tissue SAE on Day 329, resolved after 8 days, dose was interrupted, considered unrelated to study treatment by investigator.	Grade 3 abscess soft tissue AE on Day 329 (same as SAE). Grade 3 low neutrophil counts: • Day 30: 0.9×10^9/L • Day 371: 1.0×10^9/L
[redacted] Spain (17 AEs total)	19 months, female	11.0 kg	prior TCZ	Q2W	None	Grade 3 neutropenia AE on Day 69, resolved after 16 days, no dose change, considered related to study treatment by investigator.
[redacted] USA (15 AEs total)	22 months, female	11.5 kg	prior TCZ	Q2W	None	No Grade 3 AEs. Grade 3 elevated ALT: • Day 154: 172 (U/L)
<10 kg BW at baseline						
[redacted] Spain (4 AEs total)	25 months, female	9.2 kg	TCZ naive	Q10D	None	No Grade 3 AEs or laboratory abnormalities.

All of these patients completed Study WA28118 and enrolled into the LTE Study WA29231.

An analysis of steady-state Cmin values in the 3 sJIA patients < 2 years old and the patient with a BW <10 kg shows these patients have Cmin values at the higher end of exposure following treatment with TCZ SC; however, they are within the range of exposures in patients aged > 2 years in WA28118 (see section 5.3)

Safety related to drug-drug interactions and other interactions

No new data on drug interactions were provided. This is acceptable since there is no need for such data in the context of the current application.

Discontinuation due to adverse events

- **Study WA28118**

Two of 51 patients (3.9%), one in each BW group, had a total of 4 AEs (1 patient had juvenile idiopathic arthritis, and the other patient experienced oral candidiasis, pneumonia, and pulmonary haemorrhage (fatal) that led to withdrawal from study treatment (Table 14), resulting in a rate of 8.6 (95% CI: 2.3, 21.9) AEs per 100 PY in the All TCZ group.

- **LTE Study WA29231**

No patient in the LTE Study WA29231 was withdrawn due to an AE up to the clinical cut-off date.

Post marketing experience

No post marketing data with the SC formulation in sJIA are available.

2.5.1. Discussion on clinical safety

The main study contributing to the safety evaluation of TCZ SC in sJIA is the 52-week open-label Phase 1b pharmacokinetics (PK)/pharmacodynamics (PD) and safety Study WA28118. The safety analyses are based on final data from 51 sJIA patients who received TCZ SC for a total duration of 46.7 patient years (PY). The final TCZ SC safety data from Study WA28118 are compared with intravenous (IV) TCZ safety data from a data cut of the pivotal Phase III Study WA18221 (also known as TENDER), which has a comparable exposure duration and was part of the sJIA TCZ IV dossier leading to approval of the IV formulation of TCZ for sJIA patients.

Supportive data on the long-term safety of TCZ SC in patients with sJIA are provided from 37 sJIA patients in Study WA29231, the ongoing open-label long-term extension (LTE) of Study WA28118. The analyses are based on data collected up to a clinical cut-off date of 11 August 2017, which contribute an additional duration of 50.25 PYs.

The overall rate of AEs in the WA28118 All TCZ SC population was 1200.3 [95% CI: 1103.0, 1303.8] AEs per 100 PY based on a total of 561 AEs. This rate appears higher than the rate observed in the WA18221 LTE All TCZ IV population (858.8 [95% CI: 809.6, 910.2] AEs per 100 PY). The higher overall AE rate in TCZ SC Study WA28118 was partly due to a higher rate of ISRs related to the SC mode of administration, when excluding the ISR events due to the SC route of administration, the overall AE rates between TCZ SC and TCZ IV are comparable (909.3 [95%CI: 824.9, 1000.0] vs. 858.8 [95%CI: 809.6, 910.2] AEs per 100 PY). The most commonly reported AEs by SOC were Infections and Infestations (78.4%) while the most commonly reported AEs by preferred term, irrespective of treatment relationship, were viral upper respiratory tract infection and neutropenia (both 25.5%).

The overall rate of AEs in LTE Study WA29231 was 503.5 [95% CI: 443.3, 569.5] per 100 PY. This is lower than the rate in Study WA28118 (1200.3 [95% CI: 1103.0, 1303.8] AEs per 100 PY), indicating a declining trend in the rate of AEs over time in sJIA patients receiving TCZ SC.

Analysis of the WA28118 data by body weight group showed a higher AE rate in patients in the > 30 kg compared with patients in the < 30 kg (1378.7 [95% CI: 1233.5, 1536.3] vs. 1015.3 [889.1, 1154.3], respectively). The higher overall AE rate in patients weighing > 30 kg was primarily driven by higher AE rates in the SOCs General disorders and administration site conditions (mostly injection site papules which was mainly driven by a single patient who reported 39 AEs with this term), Nervous systems disorders (mostly headache), and Eye disorders (with overlapping 95% CIs; mostly iridocyclitis). Conversely, higher AE rates were observed in patients in the < 30 kg compared with patients in the > 30 kg in the Infections and Infestations (mainly upper respiratory tract infection and viral upper respiratory tract infection) and Investigations (with overlapping 95% CIs; mainly increased ALT and increased AST). Within the < 30 kg, the AE rates were similar between the Q10D dosing group (984.5 [95% CI: 767.5, 1243.9]) and the Q2W dosing group (1029.0 [877.1, 1199.7]).

In study WA28118 two patients, both weighing < 30 kg at baseline and both receiving concomitant steroids, died during the study. Both AEs leading to death were considered related to study treatment. One TCZ naive patient had a fatal AE of pulmonary haemorrhage on Day 15 after presenting with pneumonia; the patient received one dose of TCZ SC. One patient died from sepsis (serious infection) on Day 262 after having received 20 doses of TCZ SC. At the time of death, this patient weighed > 30 kg and was receiving TCZ QW. At the CHMP's request, the MAH provided the observed individual TCZ concentration-time profiles following SC regimen for these patients. Both fatalities occurred in patients who were TCZ naïve and had very low TCZ concentrations compared to other patients in the study.

In the entire TCZ IV Study WA18221, there were a total of 4 deaths (260-Week WA18221 CSR). No deaths were reported up to the clinical cut-off date of TCZ SC LTE Study WA29231.

A total of 9 SAEs were reported by 7 patients (13.7%), resulting in an SAE rate of 19.3 events per 100 PY (95% CI: 8.8, 36.6). This is consistent with incidence and rate of SAEs observed in the All TCZ IV LTE population of Study WA18221 (22.3% and 24.9 [95%CI: 17.2, 35.0] SAEs per 100 PY). A higher proportion of patients in the < 30 kg experienced an SAE in both the TCZ SC WA28118 and TCZ IV WA18221 studies compared with patients in the > 30 kg. In Study WA28118, the majority of the SAEs (5/9) were in the Infections and Infestations SOC (pneumonia [2 events], abscess soft tissue, oral candidiasis, and sepsis), which were reported in 4 patients in the < 30 kg. The most commonly reported SAEs in the All TCZ IV LTE population of Study WA18221 were also in the Infections and Infestations SOC. In the TCZ SC LTE Study WA29231, 2/37 (5.4%) patients experienced a total of 2 SAEs up to the clinical cut-off.

At least one sJIA patient experienced an AE in TCZ SC Study WA28118 or LTE Study WA29231 for the following AESI/selected AE categories: infections, serious infections, hypersensitivity reactions, ISRs, serious bleeding, neutropenia, and thrombocytopenia.

There was no increase in the rate of infection (i.e., within the Infections and infestations SOC) when comparing between the SC and IV regimens (WA28118 All TCZ SC: 258.9 [95% CI: 214.8, 309.3] vs. WA18221 LTE All TCZ IV: 280.2 [95% CI: 252.4, 310.2]). Additionally, the overall rate of infection AEs in the data cut of LTE Study WA29231 (177.1 [95% CI: 142.2, 218.0]) showed no increase in the rate of infection AEs over time in sJIA patients receiving TCZ SC. Furthermore, there was no increase in the rate of serious infections between the SC and IV regimens (WA28118 All TCZ SC: 10.7 [95% CI: 3.5, 25.0]) vs. WA18221 LTE All TCZ IV: 11.3 [95% CI: 6.34, 18.69]).

All ISRs were non-serious; the majority were Grade 1 events. The overall incidence of ISRs in Study WA28118 (sJIA patients) was higher compared with that in Study WA28117 (pJIA patients) and in Studies NA25220 and WA22762 (adult RA patients): 41.2% (WA28118) vs. 28.8% (WA28117) with TCZ SC Q3W or Q2W, 8.9% (NA25220) with TCZ SC Q2W and 12.2% (WA22762) following TCZ SC QW. In the LTE WA29231 data cut, the proportion of patients experiencing at least one ISR (8.1%) was lower compared with the core study. Although a higher incidence of sJIA patients had ISRs (in WA28118) compared with pJIA and adult RA patients, ISR symptoms were similar, with the most common being injection site erythema, injection site pain, and injection site pruritus in all three populations. No new ISR symptoms were observed.

Neutropenia AEs were reported by 25.5% of sJIA patients in Study WA28118 and by 13.5% patients in Study WA29231 following TCZ SC treatment compared with 17.9% of sJIA patients in Study WA18221 following TCZ IV treatment. The rate of neutropenia AEs overall (70.6 [95%CI: 48.6, 99.2]) were numerically higher in TCZ SC Study WA28118 compared with the corresponding rates in LTE data cut of the TCZ IV Study WA18221 (43.8 [95%CI: 33.3, 56.6]). All neutropenia events in the sJIA TCZ SC program, except 2 events, were deemed related to study treatment, but none were reported as serious or associated with a serious infection within 15 days of the neutropenia AE.

Thrombocytopenia AEs were reported by 3.9% (2/51) of sJIA patients in Study WA28118 and by 2.7% (1/37) of patients in Study WA29231 following TCZ SC treatment. There were no serious bleeding events within 15 days of a thrombocytopenia AE in the sJIA TCZ SC program. The incidence and rate of thrombocytopenia AEs were comparable between the TCZ SC and IV regimens.

No events were identified in the sJIA TCZ SC studies for the following AESI/ selected AE categories: opportunistic infections, anaphylactic reactions, serious hepatic events, serious stroke events, serious

myocardial infarction events, gastrointestinal perforations, demyelinating disorders, malignancies, and macrophage activation syndrome (MAS).

The overall incidence of NCI-CTCAE Grade > 3 post-baseline low neutrophil counts was 23.5% in TCZ SC Study WA28118 compared with 15.2% in the LTE data cut of TCZ IV Study WA18221. The incidence of Grade > 3 post-baseline low neutrophil counts was higher in patients < 30 kg compared with patients < 30 kg in the TCZ SC Study WA28118 (30.8% vs. 16.0%), which is the opposite of what was observed in the LTE data cut of TCZ IV Study WA18221(> 30 kg: 9.6% vs. < 30 kg: 18.0%). Patients who experienced Grade 3 low neutrophil count abnormalities in TCZ SC Study WA28118 generally had lower baseline neutrophil counts compared with patients who did not experience Grade 3 low neutrophil count abnormalities. There were no Grade 4 low neutrophil counts in either of the TCZ SC Studies (WA28118 and LTE WA29231), while there were two patients with Grade 4 low neutrophil counts in the LTE data cut of Study WA18221. With the exception of one patient who experienced a serious infection of soft tissue abscess within 15 days of a Grade 2 low neutrophil count, all other serious infection AEs were not within 15 days (preceding or following) a low neutrophil count. Of note, a relationship between TCZ exposure and low neutrophil counts has been slightly indicated with respect to pJIA patients.

Most sJIA patients in Study WA28118 (76.5%) and LTE Study WA29231 (70.3%) maintained a platelet count within the normal range throughout treatment with TCZ SC. All low platelet count abnormalities in TCZ SC Studies WA28118 and WA29231 were Grade 1. There were no serious bleeding events within 15 days (preceding or following) a low platelet count in either Study WA28118 or WA29231.

No patients met the laboratory criteria for Hy's Law in TCZ SC Studies WA28118 or WA29231, and there were no serious hepatic events.

In both studies, the majority of patients had ALT, AST, and bilirubin values within the normal range throughout TCZ SC treatment. The incidence of Grade > 2 LFT elevations was comparable between TCZ SC Study WA28118 and the LTE data cut of TCZ IV Study WA18221. The incidence of Grade > 2 LFT elevations reported to up to the clinical cut-off in TCZ SC LTE Study WA29231 generally decreased compared with the core study.

The majority of sJIA patients had total and LDL cholesterol levels below the elevated concentration cut points of > 200 mg/dL for total cholesterol (fasted) and > 130 mg/dL for LDL-cholesterol (fasted) throughout treatment with TCZ SC (WA28118: 66.7% and 76.6%, respectively; LTE WA29231: 83.3% and 84.4%, respectively). The proportion of patients in TCZ SC Study WA28118 with newly occurring post-baseline elevations in total cholesterol to > 200 mg/dL was comparable with that observed in the LTE data cut of the TCZ IV Study WA18221 (33.3% vs. 27.3%, respectively), whereas a higher proportion of patients from Study WA28118 had newly occurring post-baseline elevations in LDL cholesterol to > 130 mg/dL compared with that observed in the LTE datacut of WA18221 (23.4% and 12.4%, respectively). The majority of elevations in LDL cholesterol seen in WA28118, were single occurrences.

The safety profile of the 3 patients < 2 years old and the lightest patient (9.2 kg) in WA28118 was evaluated separately. Among these patients, there was 1 SAE of abscess soft tissue (patient aged 27 month at the time of the SAE; resolved after 8 days with treatment), 2 Grade 3 AEs (low neutrophil count whilst still <2 years of age, 1 in the patient who also experienced the SAE mentioned above; both events resolved following temporary interruption of TCZ, and were not associated with any serious infections), and a few sporadic Grade 3 laboratory abnormalities. All of these patients completed Study WA28118 and enrolled into the LTE Study WA29231, and the safety profile from this

group was comparable to that observed in patients > 2 years of age (BW <30 kg) on either the Q10D or Q2W dosing regimen.

Sections 4.4 and 4.8 of the SmPC have been updated to reflect the new information.

2.5.2. Conclusions on clinical safety

A robust safety analysis of study WA28118 is hampered by the small, sample size and relative short exposure for the TCZ SC patients (50.43 PY). However, the safety profile of IV TCZ is well established in pJIA.

The safety profile observed with TCZ SC 162 mg Q10D or Q2W (patients < 30 kg) and TCZ SC 162 mg QW (patients > 30 kg) was consistent with that observed with the TCZ IV regimens in Study WA18221, with the exception of ISRs due to the SC route of administration.

In study WA28118, two patients, both weighing < 30 kg at baseline and both receiving concomitant steroids, died during the study. Both fatalities occurred in patients who were TCZ naïve and had very low TCZ concentrations compared to other patients in the study.

There was no increase in the rate of SAEs with the TCZ SC regimen compared with the TCZ IV regimen.

No new or unexpected safety signals were observed.

The 3 patients < 2 years old and the lightest patient (9.2 kg) completed Study WA28118 and enrolled into the LTE Study WA29231. The safety profile from this group was comparable to that observed in patients > 2 years of age (BW <30 kg) on either the Q10D or Q2W dosing regimen.

Therefore, the overall safety profile of TCZ in sJIA from patients aged 1 year onwards and weighting at least 10 kg is considered acceptable. The SmPC has been updated to reflect this new information.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 24.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 24.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Serious infection • Complications of diverticulitis • Serious hypersensitivity reactions • Neutropenia
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 • Demyelinating disorders • Immunogenicity
Missing information	None

Pharmacovigilance plan

Study	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1	Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization			
NA	NA	NA	NA	NA
Category 2	Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances			
NA	NA	NA	NA	NA
Category 3	Required additional pharmacovigilance activities			
WA22479 (BSRBR) registry study	Prospective observational cohort studies for safety data collection.	Serious infections, Complications of diverticulitis (including GI perforation),Serious hypersensitivity reactions, Neutropenia, Thrombocytopenia and the potential risk of bleeding, Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity, Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events, Malignancies,	Ongoing	Routine updates to be provided in the scheduled PSURs. Final Switcher Report: March 2018. Final CSR Q2 2023
WA22480 (ARTIS) registry study	To provide long term safety data from the use of TCZ in Sweden for RA patients		Ongoing	Q4 2019
ML28664 (formerly	The long-term observation of		Ongoing	Q4 2018

Study	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
tracked as GA28719) (RABBIT) registry study	treatment with biologics in RA (RABBIT) in German biologics registry	Demyelinating disorders		
WA28029 (ARTHUR)	Open-label; non-controlled. Dose reduction study.	To investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients. This study collects data on efficacy, PD, and safety upon reduction of dose in patients that have minimal disease activity on their current regimen (JADAS <3.8) but are experiencing above mentioned AEs. Dose reduction is achieved by prolonging the dosing interval (from Q2W to Q3W then Q4W)	Ongoing	LPLV: Q3 2018 Final CSR: January 2020
WA29358 (Pediatrics registry study)	Observational, Safety and Effectiveness study of pJIA patients treated with TCZ	impact of TCZ therapy on the increased risk of atherosclerosis in RA patients, impact of TCZ therapy on growth development, influence on the occurrence / treatment of uveitis and to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation	Ongoing	Q1 2025
GA28720 (OTIS) pregnancy registry	Prospective, observational, exposure cohort study of pregnancy outcomes in women with RA who are exposed to tocilizumab during pregnancy compared with pregnancy outcomes of women with RA who have not used tocilizumab during pregnancy.	to monitor planned and unplanned pregnancies exposed to tocilizumab and to evaluate the possible teratogenic effect of this medication on pregnancy outcome.	Ongoing	Q4 2019
BSRBR= British Society of Rheumatology Biologics Register; CSR= Clinical Study Report; TCZ.= Tocilizumab; RA= Rheumatoid Arthritis				

Risk minimisation measures

Safety concern	Risk minimisation measures (RMM)	Pharmacovigilance activities (PhVA)
Serious infections	**Routine risk communication:** **<u>SmPC</u>** IV and SC formulation: SmPC Section 4.3 Contraindications Active, severe infections (see section 4.4) SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **<u>Patient Information Leaflet:</u>** **IV and SC Formulation** Section 2. What you need to know before you are given TCZ Section 4 Possible serious side effects: tell a doctor straightaway. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine. **Additional risk minimization measures**: Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions • Collect and analyse information on hematogenous bacterial arthritis in the sJIA population < 18 years of age **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358)
Complications of Diverticulitis	**Routine risk communication:** **<u>SmPC</u>** SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **<u>Patient Information Leaflet:</u>** Section 2 Warnings and precautions **Routine risk minimization activities recommending specific clinical measures to address the risk:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR,

Safety concern	Risk minimisation measures (RMM)	Pharmacovigilance activities (PhVA)
	Other risk minimization measures beyond the Product Information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine. **Additional risk minimization measures**: Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	ARTIS, RABBIT, WA29358)
Serious Hypersensitivity Reactions	**Routine risk communication:** **<u>SmPC</u>** SmPC section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects **<u>Patient Information Leaflet</u>** Warnings and precautions (IV formulation): Section 2 What you need to know before you are given TCZ. (SC formulation): Section 2 What you need to know before you use TCZ. Section 4 Possible Side Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures**: Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358)
Neutropenia	**Routine risk communication:**	**Routine pharmacovigilance**

Safety concern	Risk minimisation measures (RMM)	Pharmacovigilance activities (PhVA)
	<u>SmPC</u> SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects/Laboratory evaluations **<u>Patient Information Leaflet</u>** Section 4 Possible Side Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures**: Patient Brochure Healthcare Provider Brochure Dosing Guide	**activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) • WA28029 (ARTHUR)
Thrombocytopenia and the potential risk of bleeding	**Routine risk communication:** SmPC section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC section 4.2 Posology and method of administration (IV formulation) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures**: Patient Brochure Healthcare Provider Brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) • WA28029 (ARTHUR)

Safety concern	Risk minimisation measures (RMM)	Pharmacovigilance activities (PhVA)
Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity	**Routine risk communication:** **<u>SmPC</u>** SmPC section 4.2 Posology and method of administration (IV formulation) SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **<u>Patient Information Leaflet</u>** (IV/SC formulation) Section 2 Warning and precautions **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures**: Patient Brochure Healthcare Provider Brochure Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions • Pharmacogenomic analysis of patients with hyperbilirubinemia on TCZ **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) • WA28029 (ARTHUR)
Elevated Lipid Levels and Potential Risk of Cardiovascular / Cerebrovascular Events	**Routine risk communication:** **<u>SmPC</u>** SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **<u>Patient Information Leaflet</u>** Section 2 Warnings and precautions **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358)

Safety concern	Risk minimisation measures (RMM)	Pharmacovigilance activities (PhVA)
	measures: Patient Brochure Healthcare Provider Brochure Dosing Guide	
Malignancies	**Routine risk communication:** SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures**: Patient Brochure Healthcare Provider Brochure Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358)
Demyelinating Disorders	**Routine risk communication:** SmPC section 4.4 Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures**: Healthcare Provider Brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358)
Immunogenicity	**Routine risk communication:** SmPC section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Collect and analyze anti-TCZ antibodies in patients who

Safety concern	Risk minimisation measures (RMM)	Pharmacovigilance activities (PhVA)
	None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine No Additional Risk Minimization Measure	experience hypersensitivity reactions that led to study withdrawal in ongoing clinical trials and investigate the risk of developing anti-TCZ antibodies at re-administration, when TCZ treatment had been interrupted. This is specific to the ongoing clinical trials and does not apply to spontaneous post marketing cases **Additional Pharmacovigilance activities:** None
IV= Intravenous, SC= Subcutaneous; SmPC= Summary of Product Characteristics; TCZ= Tocilizumab		

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC for RoActemra 162 mg solution for injection in pre-filled syringe formulation are being updated. The Package Leaflet (PL) is updated accordingly.

In addition, sections 4.2, 4.8 and 5.2 of the SmPC of the RoActemra 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal IV study WA18221 in sJIA. The changes in Sections 4.2 and 4.8 are of purely editorial nature. The Section 5.2 of the SmPC has been updated since the information provided herein is derived from a population pharmacokinetic analysis which uses both IV and SC data. Thus, the new data obtained in Study WA28118 for sJIA SC were included in an updated popPK analysis.

The MAH has also made the following amendments in the RoActemra 20 mg/mL concentrate for solution for infusion formulation:

- Update of sections 4.8 and 5.2 to align the information on pJIA for RoActemra SC and IV (variation EMEA/H/C/955/II/72): the elevated post-baseline lipid parameters (Section 4.8) and the population PK data (Section 5.2) are updated to be consistent for RoActemra SC and IV.
- Update of the PL to implement the changes related to the new indication for the treatment of CAR T cell-induced severe or life-threatening CRS (variation EMEA/H/C/955/II/78).

Changes made to the SmPC, Labelling and Package Leaflet for RoActemra 20 mg/mL concentrate for solution for infusion formulation, RoActemra 162 mg solution for injection in pre-filled syringe formulation, RoActemra 162 mg solution for injection in pre-filled pen to bring them in line with the current QRD template and SmPC guideline were reviewed and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- No significant changes impacting the readability of the package leaflet are made.
- The key messages for safe use remain unchanged. The new additions follow the same structure and use similar descriptions and terminology as used in the current package leaflet.
- RoActemra is already approved in the JIA setting when administered intravenously; for the subcutaneous administration in JIA, user testing has been performed for pJIA (see Variation II/072).
- The target group of users does not fundamentally change: The age range of users of the SC product is essentially similar to the age range of the target user group interviewed during the RoActemra user tests of the IV product for pediatric use (sJIA/pJIA) as well as the SC product for pJIA.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Systemic juvenile idiopathic arthritis (sJIA) is a serious and potentially life-threatening disorder; associated with high morbidity and mortality, and debilitating symptoms, including spiking (quotidian) fevers, arthritis (often symmetrical and polyarticular), rash, hepatomegaly, splenomegaly, lymphadenopathy and/or serositis.

sJIA occurs throughout childhood, and can occur in children as young as 6-9 months of age. However, as the diagnosis of sJIA requires exclusion of all other possible causes, including infection, malignancy, and other rheumatic diseases, diagnosis rarely occurs before the age of 9 months, with most patients >1 year of age at diagnosis

This application provides data to support the license extension of the TCZ SC formulation in sJIA as a fixed dose of 162 mg once every 2 weeks (Q2W) for patients weighing < 30 kg and once every week (QW) for patients weighing > 30 kg. TCZ IV has already been demonstrated to be a safe and efficacious treatment for patients with sJIA in Study WA18221.

3.1.2. Available therapies and unmet medical need

The development of TCZ SC as an alternative to TCZ IV in sJIA is desirable as the administration of TCZ IV requires the placement of a peripheral line in children every 4 weeks in a healthcare setting to administer the IV infusion over 60 minutes, with all of the associated inconvenience, pain, and disruption of activities that this entails. The SC formulation of TCZ will therefore offer several tangible benefits to both sJIA patients and HCPs, including improved patient convenience, shorter administration time, no requirement for IV access (especially important for patients with poor venous

access), patient preference (choice of IV or SC route of administration), and is expected to allow for home administration of TCZ.

TCZ SC will provide an important alternative to the currently licensed TCZ IV infusion for the treatment of patients with sJIA.

There is no approved treatment for sJIA for patients aged <2 years. TCZ IV is approved for patients aged 2 years or older.

3.1.3. Main clinical studies

Data supporting the use of TCZ SC in pJIA are provided from the following studies:

- Completed Phase Ib pharmacokinetic/pharmacodynamic (PK/PD) bridging Study WA28118 (JIGSAW 118), which was designed to confirm the TCZ SC dosing regimens (selected using modelling and simulation) in patients aged 1 to 17 years old with sJIA, as well as to assess the safety of the TCZ SC formulation (efficacy was exploratory). Given the unmet medical need in sJIA <2 years of age PDCO requested the MAH to extended the age range to be studied in WA28118 from >2 years to >1 year.
- Supportive data from the completed pivotal TCZ IV Study WA18221 (TENDER), which led to approval of TCZ IV in sJIA;
- Supportive data from the ongoing, long-term extension (LTE) Study WA29231 (clinical cut-off date 11 August 2017), which is an open-label extension of the JIGSAW studies (WA28118 [sJIA] and WA28117 [pJIA]) with the aim to assess the long-term safety and efficacy of TCZ SC in pJIA and sJIA;
- Supportive data (i.e., injection site reactions [ISRs]) from the completed Phase 1b TCZ SC Study WA28117 in pJIA patients, and supportive data (i.e., ISRs) from the pivotal Phase III TCZ SC Studies WA22762 (SUMMACTA) and NA25220 (BREVACTA), which led to approval of TCZ SC in adult RA.
- Supportive data from Study NP25737, a phase I study which investigated the PK, safety and exploratory PD and efficacy of TCZ IV (12 mg/kg Q2W) in the treatment of sJIA patients aged <2 years.

3.2. Favourable effects

The results showed that patients with sJIA initiating treatment with TCZ SC experienced in both BW groups (< 30 kg and > 30 kg) improvement in all efficacy parameters measured. The overall results were consistent with those seen in the TCZ IV Study WA18221. For the patients switching from commercial TCZ IV to TCZ SC at baseline, efficacy was maintained or continued improving over the entire course of the study in both BW groups. The efficacy results from the LTE Study WA29231 showed that TCZ SC improved or maintained efficacy in the < 30 kg and the > 30 kg BW group up to Week 16 and Week 128, respectively.

The CHMP considered that the proposed dosing regimen (QW for patients > 30 kg and Q2W for patients < 30 kg) was adequate.

In patients, the TCZ SC regimen will result in PK exposures comparable to those obtained with the approved TCZ IV regimen when used to treat sJIA patients aged 1-2 years. The clinical data for the 3

patients in study WA28118 who were between 1-2 years of age at baseline support the use of TCZ SC in children aged > 1 years.

3.3. Uncertainties and limitations about favourable effects

Regarding long term efficacy assessment, limited data is available especially regarding the Q2W dosing regimen. However, the CHMP concluded that the initial SC Q10D regimen did not confer any additional efficacy benefit to sJIA patients over the proposed SC Q2W regimen, but could potentially have resulted in a worse safety profile in terms of neutropenia.

Body size is the only covariate which has an appreciable impact on the pharmacokinetics of RoActemra including elimination and absorption. The lower limit of 10 kg to start the therapy was therefore set as a precautionary step to ensure the TCZ exposure attained in these very young and vulnerable patients remains within the range seen in older children whilst still enabling access to TCZ for the majority of patients. The lower BW limit of 10.0 kg has been set regardless of age i.e. sJIA patients aged 1-2 years and ≥ 2 years. The SmPC has been updated accordingly.

3.4. Unfavourable effects

The unfavourable effects of TCZ are established: infection, allergic reactions including anaphylaxis, neutropenia, and thrombocytopenia, AST/ALT/bilirubin elevation and hypercholesterolaemia. They also include MAS in patients with sJIA.

A higher AE rate in Study WA28118 was observed partly due to the occurrence of ISRs related to the SC mode of administration.

No correlation between occurrence of serious adverse events (SAEs), any adverse event (AE), any AE Common Terminology Criteria (CTC) Grade 3 or above and AEs of the Infections and Infestations System Organ Class (SOC) and TCZ exposure (Cmin) following SC administration in sJIA could be detected by PK-PD analyses provided.

Similarly, no relationship between TCZ exposure (Cmin) and neutropenia AEs or low neutrophil count laboratory abnormalities following TCZ SC in sJIA could be identified. Of note, a relationship between TCZ exposure and low neutrophil counts has been slightly indicated with respect to pJIA patients.

There was no increase in the rate of SAEs with the TCZ SC regimen compared with the TCZ IV regimen.

No new safety signals were identified in the current study.

3.5. Uncertainties and limitations about unfavourable effects

Very limited data have been submitted in children aged 1-2 years. Two of the 3 patients experienced grade 3 low neutrophil counts whilst still <2 years of age both events resolved following temporary interruption of TCZ, and were not associated with any serious infections. One of the patients experienced at 27 months, thus at age > 2 years, a SAE which was rated unrelated. The 3 patients completed Study WA28118 and enrolled into the LTE Study WA29231, and the safety profile from this group was comparable to that observed in patients > 2 years of age (BW <30 kg).

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

TCZ IV is now a well-established treatment option for patients with sJIA. Comparable efficacy results are observed comparing the TCZ SC regimen with historical TCZ IV data in largely the same patient population.

TCZ SC is a more convenient option for sJIA patients because it requires less time to administer and is expected to allow for home administration. The availability of a TCZ SC formulation as an alternative to the currently licensed IV formulation will provide significant tangible benefits to both physicians and patients.

The higher AE rate after TCZ SC administration was observed, due in part to the occurrence of ISRs related to the SC mode of administration.

In patients, the TCZ SC regimen will result in PK exposures comparable to those obtained with the approved TCZ IV regimen when used to treat sJIA patients aged 1-2 years. The clinical data for the 3 patients in study WA28118 who were between 1-2 years of age at baseline support the use of TCZ SC in children aged > 1 years. The 3 patients completed Study WA28118 and enrolled into the LTE Study WA29231, and the safety profile from this group was comparable to that observed in patients > 2 years of age (BW <30 kg).

3.6.2. Balance of benefits and risks

The benefit-risk balance of TCZ IV for treatment of sJIA was considered previously positive. TCZ SC in children aged > 2 years shows an efficacy and safety profile comparable to the IV formulation while having the advantage of the more patient friendly administration.

In patients the TCZ SC regimen will result in PK exposures comparable to those obtained with the approved TCZ IV regimen, when used to treat sJIA patients aged 1-2 years who weigh >10.0 kg. Given the serious and potentially life-threatening complications of sJIA, the high unmet medical need for approved therapies for patients aged 1-2 years, and the well-established efficacy and safety profile of TCZ, the benefit-risk of TCZ SC therapy is considered to be overall favourable for this age group despite the very small patient number between 1 and 2 years of age (three patients).

Considering that weight is the main driver for TCZ exposure, the lower BW limit of 10.0 kg has been set regardless of age and applies for patients aged 1-2 years and aged ≥ 2. This is adequately reflected in the posology section of the SmPC.

In conclusion, the benefit-risk of TCZ SC therapy is considered to be favourable for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

3.7. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Roactemra is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication for RoActemra 162 mg solution for injection in pre-filled syringe formulation to include the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, weighting at least 10kg, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to methotrexate or where treatment with methotrexate is inappropriate) or in combination with methotrexate. This new indication is supported by the data from study WA28118, a Phase Ib, Open-Label, Multicenter Study to Investigate the Pharmacokinetics, Pharmacodynamics, and Safety of Tocilizumab Following Subcutaneous Administration to Patients sJIA. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the PL are being updated accordingly.

In addition, sections 4.2, 4.8 and 5.2 of the SmPC of the RoActemra 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal IV study WA18221 in sJIA.

The MAH has also made the following amendments in the RoActemra 20 mg/mL concentrate for solution for infusion formulation:

- Update of sections 4.8 and 5.2 to align the information on pJIA for RoActemra SC and IV (variation EMEA/H/C/955/II/72).
- Update of the PL to implement the changes related to the new indication for the treatment of CAR T cell-induced severe or life-threatening CRS (variation EMEA/H/C/955/II/78).

Changes made to the SmPC, Labelling and Package Leaflet for RoActemra 20 mg/mL concentrate for solution for infusion formulation, RoActemra 162 mg solution for injection in pre-filled syringe formulation, RoActemra 162 mg solution for injection in pre-filled pen to bring them in line with the current QRD template and SmPC guideline were reviewed and accepted by the CHMP.

Finally, the MAH has updated the RMP to implement changes related to the new indication for the treatment of CAR T cell-induced severe or life-threatening CRS (variation EMEA/H/C/955/II/78).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections

        - The product must not be given to patients with active or suspected infection
        - The product may lessen signs and symptoms of acute infection delaying the diagnosis
    - Serious injection/infusion reaction and their management
    - Serious hypersensitivity reactions and their management
    - Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
    - Reporting of serious adverse drug reactions
    - The Patient Information Packs (to be given to patients by healthcare professionals)
    - Diagnosis of Macrophage Activation Syndrome in sJIA patients
    - Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion reactions
    - Preparation of injection/infusion
    - Infusion rate
- Monitoring of the patient for injection/infusion reactions
- Reporting of serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet (with instructions for use for SC)
- Patient alert card

- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.

- to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.

- to address the risk of allergic reactions.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed

Paediatric Investigation Plan P/0266/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication for RoActemra 162 mg solution for injection in pre-filled syringe formulation to include the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, weighting at least 10kg, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to methotrexate or where treatment with methotrexate is inappropriate) or in combination with methotrexate. This new indication is supported by the data from study WA28118, a Phase Ib, Open-Label, Multicenter Study to Investigate the Pharmacokinetics, Pharmacodynamics, and Safety of Tocilizumab Following Subcutaneous Administration to Patients sJIA. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the PL are being updated accordingly.

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Finally, the MAH has updated the RMP to implement changes related to the new indication for the treatment of CAR T cell-induced severe or life-threatening CRS (variation EMEA/H/C/955/II/78).

Summary

Please refer to the scientific discussion RoActemra EMEA/H/C/000955/II/76.