Assessment report

RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0072

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

ADA   anti-drug antibody

AE   adverse event

AESI   adverse event of special interest

ALT   alanine transaminase

AST   aspartate transaminase

AUC   area under the concentration-time curve

BMI   body mass index

BSA   body surface area

BW   body weight

CHAQ-DI   Childhood Health Assessment Questionnaire-Disability Index

CI   confidence interval

CL   clearance

C_{max} maximum concentration

C_{mean} average concentration over the dosing interval

C_{min} minimum concentration

CRP   C-reactive protein

CTC   Common Terminology Criteria

DMARD   disease-modifying anti-rheumatic drug

eoJIA   extended oligoarticular juvenile idiopathic arthritis

ESR   erythrocyte sedimentation rate

EU   European Union

GCP   Good Clinical Practice

ILAR   International League of Associations for Rheumatology

IL-6   interleukin-6

IL-6R   interleukin-6 receptor

IQR   Inter Quartile Range

ITT   intent to treat

IV   Intravenous

JADAS-71   Juvenile Arthritis Disease Activity Score 71

JIA   juvenile idiopathic arthritis

Ka   absorption rate constant

KM   Michaelis-Menten constant

LDL   low-density lipoprotein

LOCF   last observation carried forward

MTX   methotrexate

NONMEM   nonlinear mixed-effect modelling

NSAID   non-steroidal anti-inflammatory drug

PD   pharmacodynamics

PFS-NSD   pre-filled syringe with a needle safety device

PIP   Paediatric Investigation Plan

pJIA   polyarticular juvenile idiopathic arthritis

PK   pharmacokinetic

Q2(3)(4)W every 2 (3) (4) weeks

QW   every week (weekly)

RA   rheumatoid arthritis

RF   rheumatoid factor

SAE   serious adverse event

SC   subcutaneous

SD   standard deviation

SE   standard error

sIL-6R   soluble interleukin-6 receptor

sJIA   systemic juvenile idiopathic arthritis

TB   tuberculosis

TCZ   tocilizumab

TNF-α   tumour necrosis factor-alpha

TU   tuberculin units

ULN   upper limit of normal

US   United States

VAS   visual analogue scale

Vc   volume of distribution of the central compartment

Vm   maximum target-mediated elimination rate

Vp   volume of distribution of the peripheral compartment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 21 July 2017 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

Extension of Indication to include "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 methotrexate" for RoActemra; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics. The Package Leaflet is updated accordingly. The Risk Management Plan version 23.0 has also been submitted.

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 not yet completed as some measures were deferred.

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.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	21 July 2017
Start of procedure	12 August 2017
CHMP Rapporteur Assessment Report	10 October 2017
PRAC Rapporteur Assessment Report	13 October 2017
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	26 October 2017
CHMP members comments	30 October 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2017
Request for supplementary information and extension of timetable adopted by the CHMP on	9 November 2017
MAH's responses submitted to the CHMP on:	22 December 2017
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	23 January 2018
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 January 2018
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	15 February 2018
PRAC RMP advice and assessment overview adopted by PRAC	8 February 2018
CHMP opinion	22 February 2018

2. Scientific discussion

2.1. Introduction

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 haematopoiesis, 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 signaling. 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 European Union (EU) both pharmaceutical forms of TCZ are approved, in combination with methotrexate (MTX), for the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults. The recommended dose for IV administration is 8 mg/kg TCZ every 4 weeks (q4w). For SC administration, the recommended dose is 162 mg once every week (qw).

The IV formulation of TCZ is also approved in the EU for the treatment of active systemic juvenile idiopathic arthritis (sJIA) and for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older. The recommended posology in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg.

TCZ can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

This application provides data to support the license extension of the TCZ SC formulation (delivered via a PFS + NSD) in pJIA as a fixed dose of 162 mg once every 3 weeks (Q3W) for patients weighing < 30 kg and once every 2 weeks (Q2W) for patients weighing $\geq$ 30 kg. TCZ IV has already been demonstrated to be a safe and efficacious treatment for patients with pJIA in Study WA19977.

The development of TCZ SC as an alternative to TCZ IV in pJIA is desirable because 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 pJIA 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.

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

- Completed Phase Ib pharmacokinetic/pharmacodynamic (PK/PD) bridging Study WA28117 (JIGSAW 117), which was designed to confirm the TCZ SC dosing regimens (selected using modelling and simulation) in patients aged 1 to 17 years old with pJIA, as well as to assess the safety of the TCZ SC formulation (efficacy was exploratory)

- Supportive data from the completed pivotal TCZ IV Study WA19977 (CHERISH), which led to approval of TCZ IV in pJIA;

- Supportive data from the ongoing, long-term extension (LTE) Study WA29231 (clinical cut-off date 17 July 2016), which is an open-label extension of the JIGSAW studies (WA28117 [pJIA] and WA28118 [sJIA]) with the aim to assess the long-term safety and efficacy of TCZ SC in pJIA and sJIA; and

- Supportive data (i.e., injection site reactions [ISRs and PK]) from the completed pivotal Phase III TCZ SC Studies WA22762 (SUMMACTA) and NA25220 (BREVACTA), which led to approval of TCZ SC in adult RA.

Background on disease

Juvenile idiopathic arthritis is a broad term that describes a clinically heterogeneous group of arthritis of unknown aetiology that begins before the age of 16 years and persists for at least 6 weeks. The International League of Associations for Rheumatology (ILAR) has classified JIA into seven subtypes (Petty et al. 2004): systemic arthritis, oligoarthritis (persistent or extended), polyarthritis (rheumatoid

factor [RF] positive or negative), psoriatic arthritis, enthesitis related arthritis, and undifferentiated arthritis. The term pJIA in this application is used to refer to the following JIA ILAR categories: RF-positive polyarthritis, RF-negative polyarthritis, as well as patients with extended oligoarthritis (eoJIA). The same definition of pJIA was used for both the TCZ SC Study WA28117 and TCZ IV Study WA19977.

Patients with RF-positive and RF-negative pJIA present with 5 or more active joints in the first 6 months of the disease (Petty et al. 2004). For patients in the RF-positive subset, which comprises approximately 15% of polyarthritis cases, the disease is defined as two or more positive tests for RF at least 3 months apart (Rosenberg AM and Oen KG 2011). RF-positive JIA is considered to be the subset most closely related to adult RA. Although large joints are commonly involved, the characteristic pattern of articular disease is symmetrical arthritis affecting the hands, wrists, and feet. The predominant extra-articular manifestation of RF-positive disease is rheumatoid nodules.

In patients with RF-negative disease, articular disease is the predominant clinical manifestation with the knees, wrists, and ankles being the most commonly affected joints although small joint involvement of the hands and feet is not uncommon (Naidu et al. 2000). Systemic manifestations in patients with seronegative disease are uncommon but can include fatigue and growth failure.

Oligoarticular pJIA is characterized by arthritis of one to four joints during the first 6 months of the disease and is sub-classified as eoJIA if more than 4 joints are affected after the initial 6 months. eoJIA is primarily a disease of the lower extremities at the time of diagnosis, although involvement of the wrists and the small joints of the hands and feet can be present at diagnosis or can evolve over the course of the disease.

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

The EMA 2006 Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products [EMEA/CHMP/SWP/4447/00 corr. 2] requires an ERA for the Marketing Authorisation Application (MAA) of all new medicinal products in the European Union. For proteins and peptides, however, the 'ERA may consist of a justification for not submitting ERA studies, *e.g.,* due to their nature they are unlikely to result in a significant risk to the environment.

The active pharmaceutical substance Tocilizumab is a monoclonal antibody, a large human-specific protein. Considering human metabolism, rapid biodegradability and acute ecotoxicological properties of Tocilizumab, no exposure levels of concern to the environment are to be expected.

2.2.2. Discussion on non-clinical aspects

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

No formal ERA according to the EMA 2006 Guideline (corr. 2) is needed for Tocilizumab.

2.2.3. Conclusion on the non-clinical aspects

This application is considered acceptable from a non-clinical point view.

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

Study No.	Study Design	Dose and Regimen	Study Objectives	No. of Patients	Status
Phase 1b PK/PD Bridging Study:					
WA28117 (Phase 1b)	Open-label, multicenter study to investigate the PK, PD, and safety of TCZ following SC administration to patients with pJIA aged 1 to 17 years	BW < 30 kg: 162 mg TCZ SC Q3W BW ≥ 30 kg: 162 mg TCZ SC Q2W	Characterize the PK, evaluate the PD and safety, and describe the efficacy (exploratory) of TCZ SC in patients with pJIA	N = 52	Completed
Supportive Studies:					
WA19977 (Phase 3)	Two-year, three-part study in patients with active pJIA aged 2 to 17 years **Part I:** 16-week open-label lead-in phase **Part II:** 24-week randomized double-blind, placebo controlled withdrawal phase **Part III:** 64-week open-label treatment phase	**Part I:** BW < 30 kg: 8 or 10 mg/kg TCZ IV Q4W BW ≥ 30 kg: 8 mg/kg TCZ IV Q4W **Part II:** TCZ IV (same dose regimens as Part I) or placebo IV Q4W. **Part III:** TCZ IV (same dose regimens as Part I).	Evaluate the efficacy of open-label TCZ IV (Part I), compare the proportion of patients on TCZ vs. placebo who developed a JIA ACR30 flare (compared to Week 16) by Week 40 (Part II), evaluate the long-term effect of TCZ on the maintenance of clinical response and safety in patients with pJIA (Part III), evaluate the efficacy and safety of 8 mg/kg vs. 10 mg/kg in patients < 30 kg (Parts I, II and III)	Part I: N = 188 Part II: N = 166 Part III: N = 160	Completed
WA29231 (Phase 1b, LTE)	Long-term extension study for WA28117 (pJIA) and WA28118 (sJIA) (maximum of 3 additional years of treatment) to evaluate the safety and efficacy of TCZ SC in patients with pJIA and sJIA[b]	For pJIA: BW < 30 kg: 162 mg TCZ SC Q3W BW ≥ 30 kg: 162 mg TCZ SC Q2W	Evaluate the long-term safety and efficacy of TCZ SC in patients with pJIA and sJIA[b]	N = 41[a]	Ongoing

BW = body weight; LTE = long-term extension; IV = intravenous; JIA ACR = juvenile idiopathic arthritis American College of Rheumatology; PD = pharmacodynamic; pJIA = polyarticular juvenile idiopathic arthritis; PK = pharmacokinetic; Q2W = every 2 weeks; Q3W = every 3 weeks; Q3W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] Enrollment as of 17 July 2016. Note that three additional pJIA patients were enrolled after the cutoff; thus, in total, 44 of the 46 patients who completed Study WA28117 enrolled in LTE Study WA29231. [b] Only data from patients with pJIA are summarized in this dossier.

Further supportive data (i.e., injection site reactions [ISRs and PK]) from the completed pivotal Phase III TCZ SC Studies WA22762 (SUMMACTA) and NA25220 (BREVACTA), which led to approval of TCZ SC in adult RA are also provided.

2.3.2. Pharmacokinetics

Statistical methods

Nonlinear mixed-effect modelling (NONMEM) was used to analyse the sparse serum concentration−time data for TCZ. The PK data from this study was planned to be pooled and analysed with the IV data obtained from Study WA19977. Population PK and individual PK parameters were estimated and the influence of various covariates on these parameters was investigated. Details and results of modelling analyses will be reported separately.

PK modelling and data analysis

PK data

There were two clinical studies in the clinical development program for TCZ in pJIA from which PK and PD data has been collected. The clinical PK of TCZ was characterized using the population PK approach which includes 237 paediatric pJIA patients from Studies WA28117 (JIGSAW 117, n = 52) and WA19977 (Cherish, n = 188) resulting in a total PK data set of 3484 serum samples for population PK analyses.

- In the completed 2-year Phase III Study WA19977, patients who weighed <30 kg received TCZ IV Q4W at a dose of either 10 mg/kg or 8 mg/kg, and patients who weighed ≥ 30 kg received TCZ IV Q4W at a dose of 8 mg/kg. 2653 samples have been collected and included in pJIA population PK analysis.

- Study WA28117 was a Phase Ib bridging study in paediatric patients with pJIA, aged 1 to 17 years old (12 to 17 years for patients in Russia), to identify the SC dose regimen or regimens that achieve comparable PK/PD and safety profiles to the IV regimens established in Study WA19977. Patients weighing <30 kg (n = 27) were dosed with 162 mg of TCZ every 3 weeks (Q3W), and patients weighing ≥ 30 kg (n=25) were dosed with 162 mg of TCZ every 2 weeks (Q2W). The dosing interval of TCZ could be adjusted according to changes in BW after Week 14. The dosing interval of SC 162 mg administration of TCZ for this study has been selected based on the following bridging strategy. 831 samples have been collected and analysed in the overall pJIA population PK study.

  Serum PK samples were obtained according to the following schedule:

  For patients weighing < 30 kg and < 2 years old:
  Pre-dose, Day 4, 21, 42, 84, 84.25, 86, 88, 90, and 105;

  For patients weighing < 30 kg and > 2 years old:
  Pre-dose, Day 0.25, 0.5, 2, 5, 21, 42, 84, 84.25, 84.5, 86, 88, 90, and 105;

  For patients weighing > 30 kg:
  Pre-dose, Day 0.25, 0.5, 2, 5, 14, 28, 42, 84, 84.25, 84.5, 86, 88, 90, and 98.

In the bridging study, 12 (1.4%) non-BQL and 22 (2.5%) post dose BQL samples have been excluded from the population PK analysis.

Bridging strategy

A population PK model was previously developed for the IV formulation for the pJIA population based on data from Study WA19977. By combining the population PK model developed for the IV formulation along with prior knowledge on the SC absorption obtained from the adult RA population, PK profiles for different SC dose regimens were simulated for pJIA patients.

Steady-state C_{min} has been established as the primary PK driver of efficacy for bridging between indications and formulations for TCZ. This C_{min} strategy was successfully applied to bridge from the approved IV dose regimen to the SC dose regimen for adult rheumatoid arthritis (RA) and from the approved IV dose regimen in adult RA to the IV dose regimens subsequently approved for pJIA and systemic juvenile idiopathic arthritis (sJIA).

The steady-state C_{min} simulated for the different SC dose regimens were compared with the steady-state C_{min} achieved from the 8 mg/kg (BW ≥ 30 kg) and 10 mg/kg (BW < 30 kg) Q4W IV regimens. Based on the simulation results, the 162 mg Q2W (BW ≥ 30 kg) and 162 mg Q3W (BW < 30 kg) TCZ SC regimens were recommended for pJIA patients because, with these dose regimens, most of the patients were

predicted to achieve a steady-state C_{min} above the 5th percentile (i.e., p5th) of that achieved by the TCZ IV formulation, across the body weight spectrum for pJIA patients.

Study WA28117:

831 sparse TCZ samples have been collected from the bridging from 52 patients aged 1 to 17 years. The median observed PK concentration-time profiles of TCZ following 52 weeks of treatment in TCZ naïve and prior TCZ patients are shown in the figure below.

Figure 1 - Median observed PK concentration-time profiles of TCZ (μg/mL) over 52 weeks of SC treatment versus nominal time (weeks)
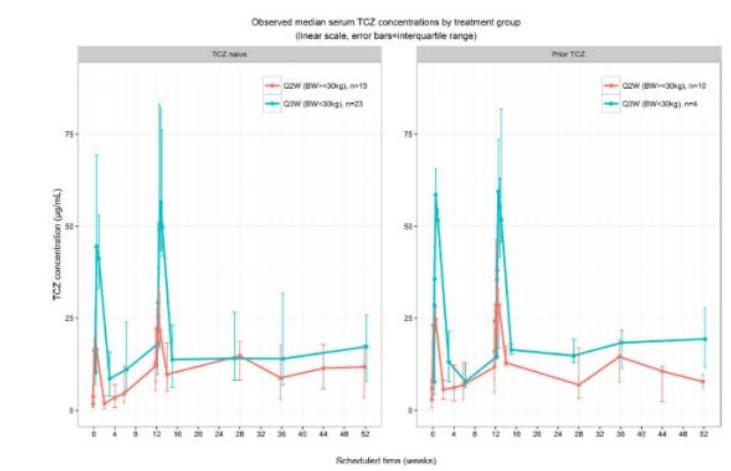
Figure 2 - Observed tocilizumab serum concentrations (µg/mL) versus nominal time (weeks) after IV application (top) and SC application (bottom). Red lines indicate patients from Study WA28117 with prior IV exposure.
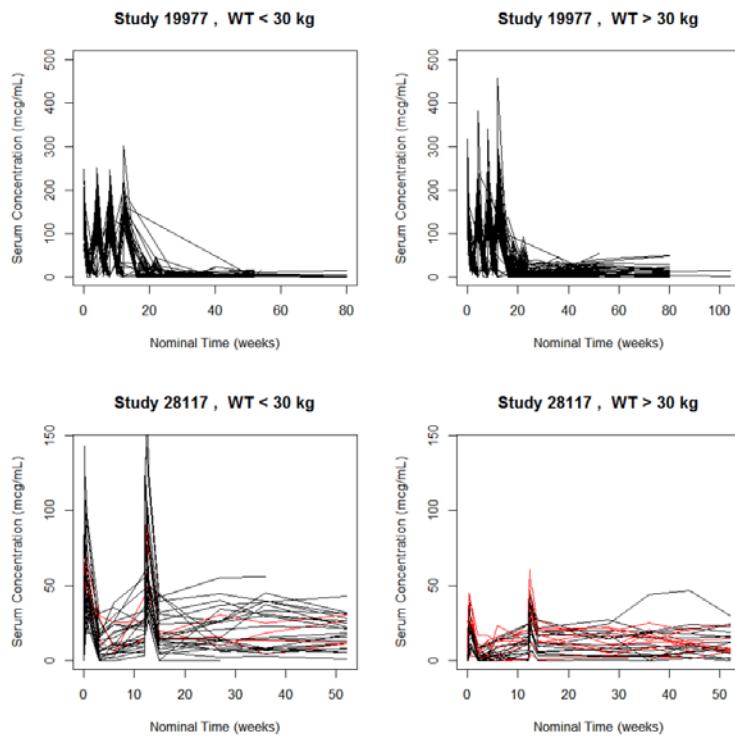
The median TCZ concentration profiles were higher for patients weighing < 30 kg compared to those weighing ≥ 30 kg. For TCZ naive patients, the observed median C_{min} (range) was 20.0 (3.4 - 55.6) µg/mL at Week 12 and 18.6 (3.0-55.9) mg/mL at Week 36 for the <30 kg BW group, and 12.1 (0.6-24.5) µg/mL and 8.8 (0.3-44.1) µg/mL for the ≥ 30 kg BW group, respectively.

For prior TCZ patients, the observed median C_{min} (range) was 14.6 (13.2-25.9) µg/mL at Week 12 and 18.3 (4.3-25.1) µg/mL at Week 36 for the < 30 kg BW group and 12.4 (0.4-28.3) µg/mL and 15.8 (3.3-25.0) µg/mL for the ≥ 30 kg BW group, respectively.

Population PK model

Individual PK parameters estimated for each patient were used to compute secondary PK parameters such as AUC, C_{max}, and C_{min} at steady state. All PK parameters were to be presented in listings and descriptive summary statistics, including the arithmetic mean, median, range, standard deviation (SD), and coefficient of variation. Major baseline covariates were to be identified and the dependence of PK parameters on each covariate were to be described.

A two-compartment PK model with parallel linear and Michaelis-Menten eliminations, and first-order absorption to describe SC administration was selected to describe the PK of TCZ. The structural model used to describe the PK of TCZ for pJIA is the same as that used to describe the PK of TCZ in adult RA patients.

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, VM, and Ka.

The following final PK estimates have been calculated after covariates have been selected. These are discussed below (Section special populations). Individual PK parameters estimated for each patient were used to compute secondary PK parameters such as AUC, C_{max}, and C_{min} at steady state.

Model Evaluation

The predictive performance of the final popPK model was evaluated by graphical evaluations (e.g., observed concentrations versus population and individual predictions, conditional weighted residuals versus time and population predictions, individual weighted residuals versus individual predictions and time, etc.), precision of the parameter estimates, visual predictive check, predictive check simulations, and normalized prediction distribution errors.

Figure 3 - Comparison of Individual Predictions with Observed Data for the final model, stratified by Route of Administration and Weight Group

Circles show the observed concentrations. The dashed and solid lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations and individual predictions (IPRED), respectively. Group: 0 = WT < 30 kg, 1 = WT > 30 kg.
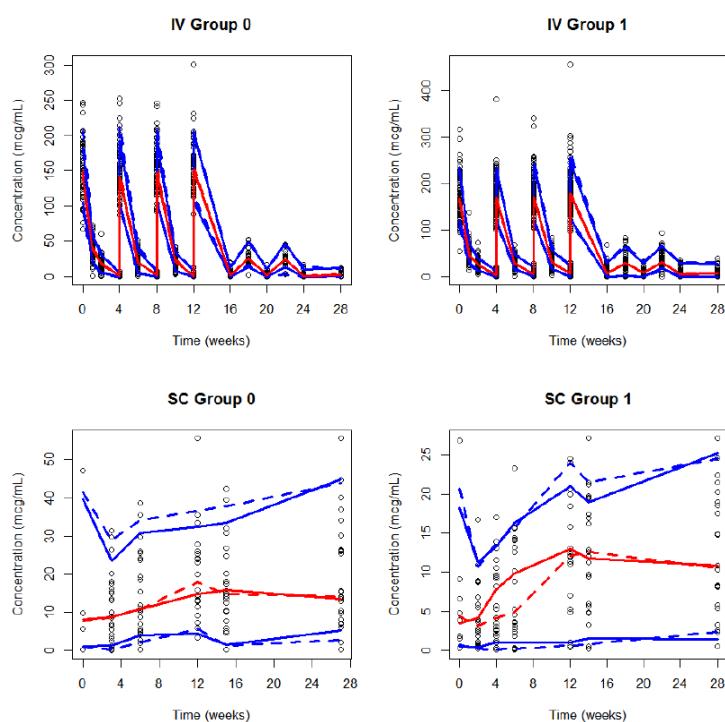
Figure 4 - Visual Predictive Check (with Confidence Intervals) for the final model, by Route of Administration and Weight Groups
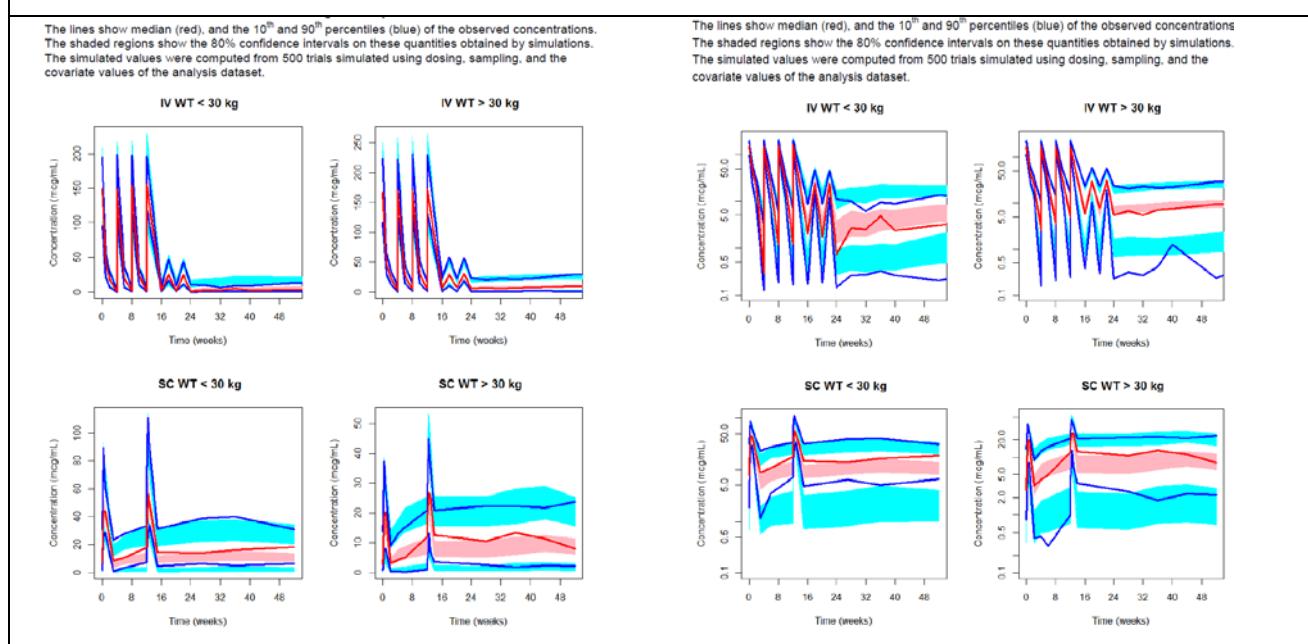
Absorption

The bioavailability estimated for a typical pJIA patient with a BMI of 18 is 96.4%, which is higher compared to that estimated for adult RA patients (79.5%). This difference in bioavailability of TCZ SC between paediatric 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.

During covariate selection, BMI was also identified to have a significant impact on the SC absorption parameters Ka and FSC, with decreasing Ka and FSC correlated with increasing BMI.

Distribution

Volume of distribution has been estimated using population PK analysis 4L.

Elimination

Due to dependency 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 3.5 and 10.3 days for the 162 mg Q3W 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 3.1 and 7.1 days for the 162 mg Q2W regimen.

Linear clearance has been estimated to 0.150 L/day, non-linear clearance is characterized by Vm = 5.81 mg/L/day and Km = 0.462µg/mL.

Dose proportionality and time dependencies

Using the individual Bayesian post hoc parameters estimated by the final popPK model, concentration-time profiles were simulated for all pJIA patients included in the popPK analysis based on per protocol dosing. Simulations of the population concentration-time profiles showed that the concentration following the Q3W SC regimen was higher compared to the Q2W SC regimen (Figure and Table below) due to the influence of body weight/size.

The accumulation ratios for C_{trough} are 3.58 and 2.08 for TCZ 162 mg Q2W and Q3W SC regimens, respectively; for AUC_{tau} and average concentration over the dosing interval (C_{mean}), these ratios are 2.04 and 1.46, respectively. Approximately 90% of the steady-state exposure levels were reached after the 6th SC injection in Q2W regimen, and after the 4th SC injection in Q3W regimen.

Table 1 - Accumulation Ratios following SC and IV Regimens

Dosing Regimen	Accumulation ratio [a]			
	AUC_T	C_{mean}	C_{max}	C_{trough}
SC Regimens				
WT >= 30 kg, 162 mg SC Q2W	2.04	2.04	1.72	3.58
WT < 30 kg, 162 mg SC Q3W	1.46	1.46	1.32	2.08
IV Regimens				
WT >= 30 kg, 8 mg/kg Q4W	1.18	1.18	1.06	2.30
WT < 30 kg, 10 mg/kg Q4W	1.06	1.06	1.03	1.78

[a] Ratio of the means for the last to the first dosing interval from conditional simulations

Observed C_{min_ss} achieved in the LTE study over 72 weeks (median C_{trough}: 21.42µg/mL (<30 kg BW group) and median C_{trough}: 4.82 µg/mL in the BW group ≥30 kg) are within the range of steady-state C_{min_ss} achieved in WA28117 for both applied regimens.

Table 2 - Simulated TCZ concentration-time profiles for PJIA paediatric patients
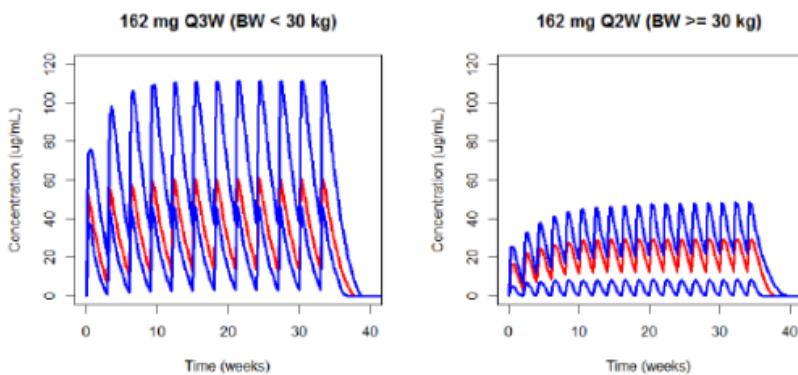
Median (red) and 90% prediction intervals (blue) of the simulated concentration-time profiles following 162 mg TCZ administered SC, Q2W, or Q3W. For each dosing regimen, concentrations were simulated for patients from Study WA28117.

Dosing Regimen	N	Median BW (min–max) (kg)	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{12weeks}$ (µg/mL • day)	C_{mean} (µg/mL)
162 mg SC Q3W BW <30 kg	27	20.0 12.0–28.0	18.38±12.87 13.35 (0.21–52.25)	75.46 ± 24.1 62.44 (39.37–121.13)	3826±1164 2998 (1465–7708)	45.54 ± 19.81 35.69 (17.44-91.76)
162 mg SC Q2W BW ≥30 kg	25	54.7 34.2–97.9	11.79±7.08 12.71 (0.19–23.75)	29.37±13.54 29.74 (7.56–50.3)	1821±873 1933 (324–3098)	21.68 ± 10.39 23.01 (3.86-36.89)

Note: For C_{min}, C_{max}, $AUC_{12weeks}$, and C_{mean}, the mean±SD is presented on top, with the median and (range) presented below.
AUC=area under the concentration-time curve; BW=body weight; C_{max}=maximum concentration; C_{min}=minimum concentration; C_{mean}=mean concentration; Q2(4)W=every 2(4) weeks; SC=subcutaneous.

Comparison to intravenous administration of TCZ in pJIA subjects

These model-computed steady state exposure PK parameters for TCZ in pJIA have been compared by IV and SC regimen as summarized below.

Table 3 - Summary of Model-Computed Steady-State Exposure Parameters for TCZ in pJIA by Regimen

Dosing Regimen	n	Body Weight (kg) median min−max	C_{min} (µg/mL) mean±SD median (min−max)	C_{max} (µg/mL) mean ± SD median (min−max)	$AUC_{12weeks}$ (µg/mL • day) mean ± SD median (min−max)	C_{mean} (µg/mL) mean±SD median (min−max)
TCZ SC in pJIA						
162 mg SC Q3W BW <30 kg	27	20.0 12.0–28.0	18.38±12.87 13.35 (0.21–52.25)	75.46 ± 24.1 62.44 (39.37–121.13)	3826±1164 2998 (1465–7708)	45.54 ± 19.81 35.69 (17.44–91.76)
162 mg SC Q2W BW ≥30 kg	25	54.7 34.2–97.9	11.79±7.08 12.71 (0.19–23.75)	29.37±13.54 29.74 (7.56–50.3)	1821±873 1933 (324–3098)	21.68 ± 10.39 23.01 (3.86–36.89)
TCZ IV in pJIA						
10 mg/kg IV Q4W BW <30 kg	35	20.9 9.6–29.5	1.47±2.44 0.35 (0–11.81)	168.37±24.84 166.61 (125.44–219.64)	2656±658 2586 (1341–4035)	31.61 ± 7.84 30.79 (15.96–48.04)
8 mg/kg IV Q4W BW ≥30 kg	119	48.4 30.7–85.1	6.55±7.93 3.28 (0.02–35.4)	182.96±42.32 181.15 (114.46–330.52)	3543±1126 3244 (1862–7038)	42.18 ± 13.4 38.62 (22.16–83.79)

Note: The corresponding SC and IV BW treatment regimens from Study WA28117 and Study WA19977 are highlighted with matching colors.
AUC=area under the concentration-time curve; BW=body weight; C_{max}=maximum concentration; C_{min}=minimum concentration; IV=intravenous; Q2(3)(4)W=every 2(3)(4) weeks; SC=subcutaneous; SD=standard deviation.

Model-Computed Steady-State Cmin by Regimen

Model-Computed Steady-State 12-Week AUC by Regimen
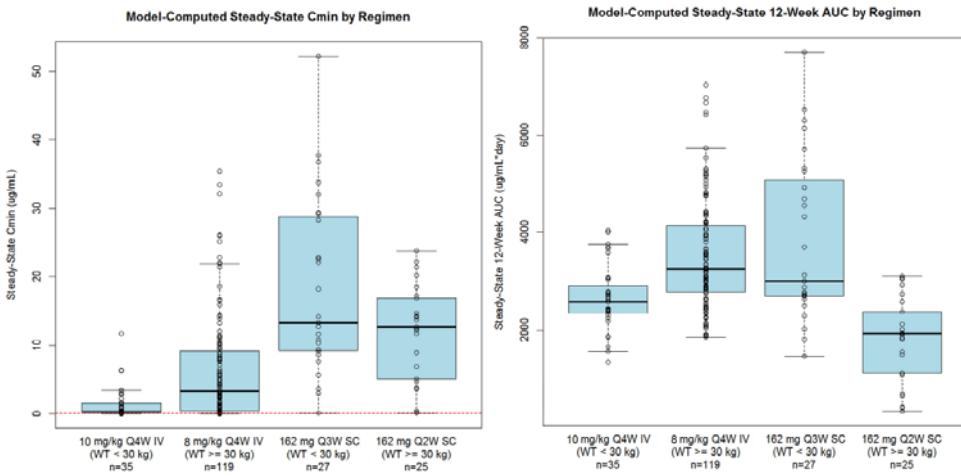
Comparison of steady state exposure following SC administration of TCZ in pJIA and adult RA subjects

At steady-state, the range of C_{min} achieved by the 162 mg SC Q3W (BW < 30 kg) and the 162 mg SC Q2W (BW ≥ 30 kg) regimens in pJIA patients are within the range of that achieved by the 162 mg SC Q2W and 162 mg SC QW regimens in adult RA patients (see below). The majority of the pJIA patients (59.8% for BW < 30 kg and 72.7% for BW ≥ 30 kg) fall within the 5th and 95th percentiles of the adult RA Q2W regimen, and 57.5% of pJIA patients with BW < 30 kg and 41.3% of pJIA patients with BW ≥ 30 kg that fall within the 5th and 95th percentiles of the adult RA QW regimen.

The range of $AUC_{ss,0-12weeks}$, and steady-state C_{max} achieved by the 162 mg SC Q3W (BW < 30 kg) and the 162 mg SC Q2W (BW ≥ 30 kg) regimens in pJIA patients are also within the range of that achieved by the 162 mg SC Q2W and 162 mg SC QW regimens in adult RA patients.

Table 4 - Model-Computed Steady-State Exposure Parameters for pJIA Patients and for Adult RA Patients

Indication/Dosing Regimens	n	Body Weight (kg) median min−max	C_{min} (µg/mL) mean±SD median (min−max)	C_{max} (µg/mL) mean±SD median (min−max)	$AUC_{12weeks}$ (µg/mL•day) mean±SD median (min−max)	C_{mean} (µg/mL) mean±SD median (min−max)
pJIA						
162 mg SC Q3W BW < 30 kg	27	20.0 12.0–28.0	18.38±12.87 13.35 (0.21–52.25)	75.46±24.1 62.44 (39.37–121.13)	3826±1164 2998 (1465–7708)	45.54 ± 19.81 35.69 (17.44–91.76)
162 mg SC Q2W BW ≥ 30 kg	25	54.7 34.2–97.9	11.79±7.08 12.71 (0.19–23.75)	29.37±13.54 29.74 (7.56–50.3)	1821±873 1933 (324–3098)	21.68 ± 10.39 23.01 (3.86–36.89)
Adult RA						
162 mg SC Q2W	509	67.0 37.1–132	5.9±6.3 4.1 (0–34.4)	13.0±8.3 11.1 (0.4–48.7)	865.2±633 720 (18–3645)	10.3 ± 7.5 8.6 (0.2 – 43.4)
162 mg SC QW	621	72.0 34.4–149	45.3±22.2 43.1 (1.3–145.2)	51.3±23.2 49.6 (2.9–150.1)	4127±1916 3990 (195.6–12460)	49.1 ± 22.8 47.5 (2.3 – 148.3)

SD=standard deviation.

Figure 5 - Simulated Steady-State PK Concentration-Time Profiles and C_{min} for pJIA and Adult RA Patients Following SC TCZ Regimens
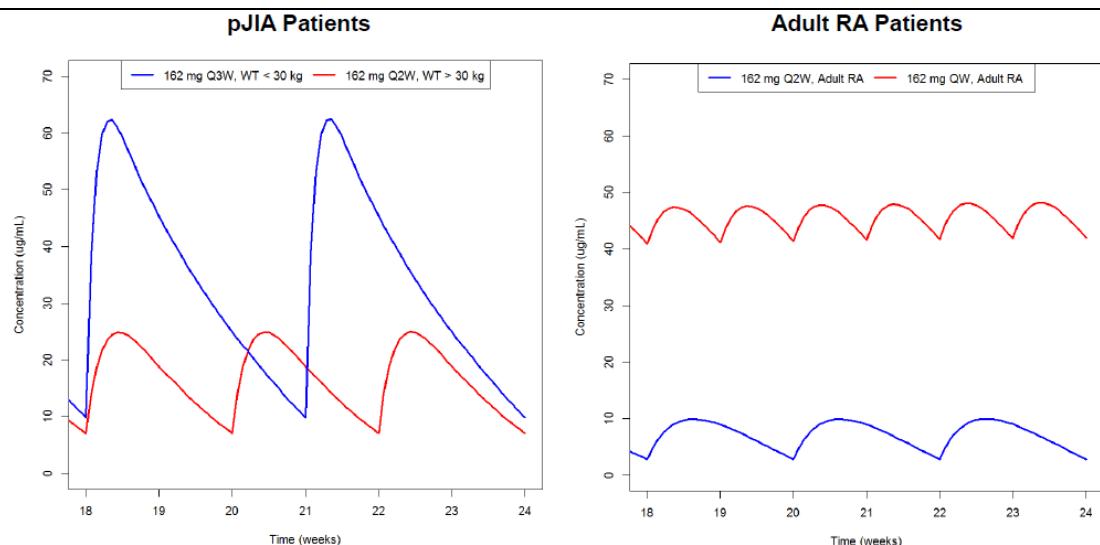
Median PK concentration-time profiles are shown for pJIA patients from each body weight group. For adult RA patients, the PK concentration-time profiles are shown for a typical adult RA patient of 75 kg.

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. The red dash line denotes the model computed p5[th] from Study WA19977.
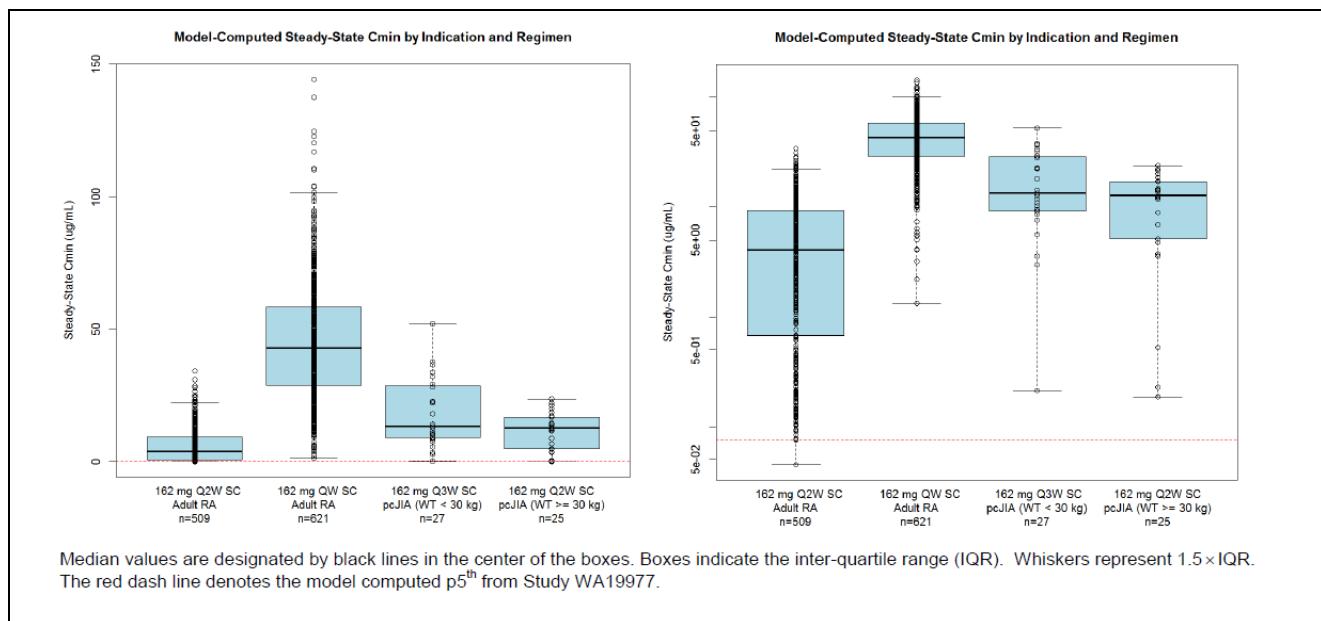
Special populations

Patient population characteristics

Demographic and disease characteristics at baseline were as expected in this paediatric patient population and were overall well balanced between BW groups. The two BW groups (< 30 kg vs. ≥ 30 kg) differed in median age (6.0 years vs. 15.0 years), median height (111.8 cm vs. 165.4 cm), and median weight (20.0 kg vs. 54.7 kg), which is expected for these BW-based groups. There was 1 patient under the age of 2 years at baseline and no patient weighed >100 kg.

Table 5 - Summary of continuous covariates (median and range) and categorical covariates

Covariate	Units	Total	WA19977	WA28117
N		237	188	52
WT	kg	38.6 [9.6 - 97.9]	39.2 [9.6 - 85.1]	27.2 [12 - 97.9]
BMI	kg/m²	17.9 [11.9 - 35.4]	18.3 [11.9 - 35.4]	17 [13 - 35]
BSA	m²	1.24 [0.471 - 2.06]	1.25 [0.471 - 1.98]	0.985 [0.55 - 2.06]
AGE	years	11 [1.92 - 17.7]	11 [2 - 17]	8.88 [1.92 - 17.7]
SCRT	µmol/L	44 [18 - 82]	43 [19 - 82]	44 [18 - 80]
CRCL	mL/min	117 [53.8 - 256]	121 [53.8 - 250]	113 [55.7 - 256]
HT	m	1.42 [0.85 - 1.8]	1.43 [0.85 - 1.8]	1.31 [0.92 - 1.72]

Covariate	Levels	Number of Subjects (Percent)		
		Total	WA19977	WA28117
STUDY	WA19977	188 (78.3%)	188 (100%)	-
	WA28117	52 (21.7%)	-	52 (100%)
GRP	IV only	-	188 (100%)	-
	SC with no prior IV	-	-	38 (73.1%)
	SC with prior IV	-	-	14 (26.9%)
WTGRP	0: WT < 30 kg	96 (40%)	69 (36.7%)	27 (51.9%)
	1: WT > 30 kg	144 (60%)	119 (63.3%)	25 (48.1%)
SEX	0: Female	180 (75%)	144 (76.6%)	36 (69.2%)
	1: Male	60 (25%)	44 (23.4%)	16 (30.8%)
HAHA	-99: missing	-	188 (100%)	-
	0: not detected	-	-	49 (94.2%)
	1: detected at least once	-	-	3 (5.8%)

Covariate selection

Based on prior knowledge from the previous population PK analysis using only IV data from pJIA patients, the popPK model contained BSA on linear CL, height on Vc, BSA on Vp, and both BSA and serum creatinine on VM as covariates.

This model was used as the starting point of the population PK analysis. Covariate effects identified for pJIA patients in the previous analysis using only 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. Distributions of the random effects for patients with and without detected ADA were compared, and the effects of ADAs were also tested as time-dependent covariates on linear and Michaelis-Menten clearances.

Consistent with the knowledge on the PK of TCZ in other indications, body size parameters (height, BSA, and BMI) were the most significant covariate in explaining the variability in the PK for TCZ in pJIA: BSA on linear CL, Vp, and VM, and height on Vc.

BMI was also identified to have a significant impact on the SC absorption parameters Ka and FSC, with decreasing Ka and FSC correlated with increasing BMI.

Body weight/size

In contrast to the other investigated covariates, body size has an appreciable impact on the PK of TCZ.

2.3.3. Pharmacodynamics

Mechanism of action

The antibody TCZ binds specifically to both sIL-6R and membrane-bound IL-6R to inhibit IL-6R-mediated signalling.

Primary and secondary pharmacology

Primary pharmacology

sIL-6R: Based on the known mode of action, there is an increase in serum antibody-sIL-6 receptor complexes in patients following treatment with TCZ (see figure below).

Figure 6 - sIL-6R Over Time by Regimen and by Prior TCZ Status
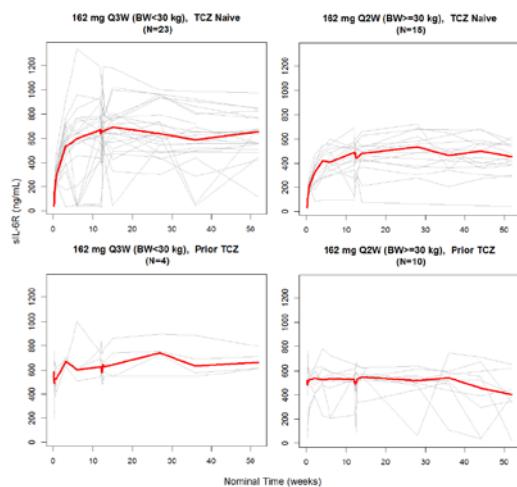
Observed values over time (thin gray lines) for patients in Q3W (left) or Q2W (right) TCZ treatment arms that are TCZ naive (top) or received TCZ previously (bottom). Red bold lines are medians.

IL-6:
In addition, IL-6 concentration-time profiles by regimen have been provided as shown below. For TCZ naive patients, the IL-6 concentration increased rapidly one week following the first dose with subsequent fluctuations but low median IL-6 in the following.

Figure 7 - IL-6 over Time by Regimen and by Prior TCZ Status
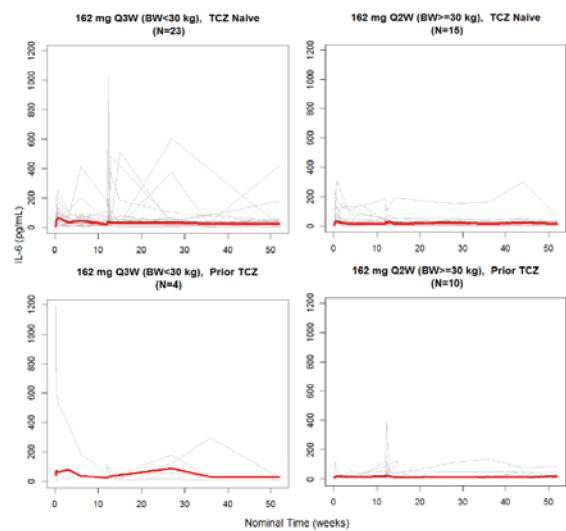
The observed CRP and ESR concentration-time profiles by regimen for both TCZ naive and prior TCZ paediatric subjects have been assessed as shown below. Following administration of TCZ SC for naive patients, a rapid and similar decline was observed in the CRP and ESR concentration levels and remained low from Week 6 through week 52 for both regimen with a higher variability observed in the naïve subgroups.

C - reactive protein (CRP):

Figure 8 - CRP over Time by Regimen and by Prior TCZ Status Observed
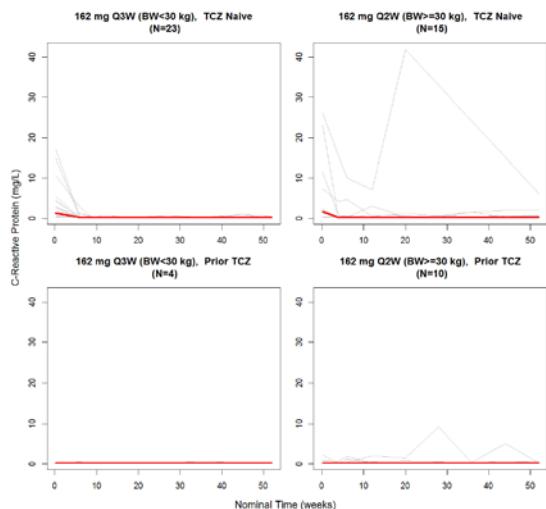
Erythrocyte Sedimentation Rate (ESR):

Figure 9 - ESR over Time by Regimen and by Prior TCZ Status
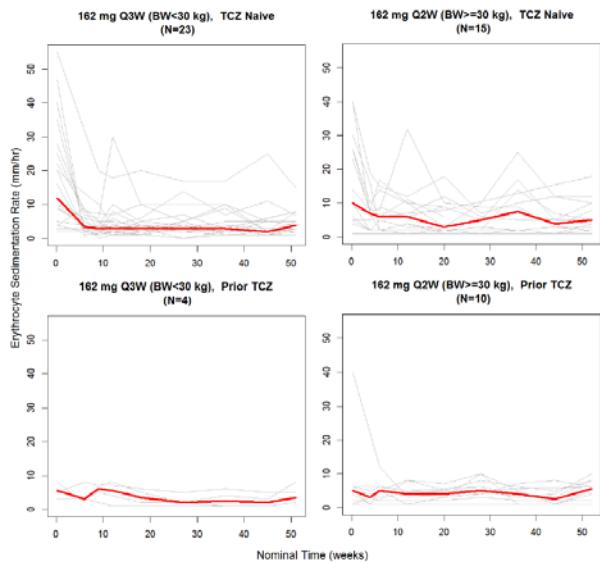
Exposure-ADA Relationship:

All 52 patients had a screening assay result at baseline and at least one post-baseline. At baseline, no patient was positive in the confirmation assay.

Post-baseline, 3 out of 52 patients (5.8%, 1 patient < 30 kg following Q3W regimen and 2 patients ≥ 30 kg following Q2W regimen) developed treatment-induced ADA after TCZ treatment in the study. All ADAs had neutralizing potential, but none were of the IgE isotype. All 3 patients were TCZ naive at study entry, and the ADA developed more than 200 days after starting treatment. None of these 3 patients missed either their TCZ SC Q3W or Q2W dose prior to becoming ADA positive.

Population PK analysis was used to assess the effect of ADA on the PK of TCZ in pJIA patients. While the serum TCZ concentrations for these 3 ADA positive patients appeared to be slightly lower compared to those patients who were not ADA positive, their observed TCZ concentrations were within the range of those patients who were not ADA positive.

2.3.4. PK/PD modelling

Methodology

Graphical exposure-safety and exposure-efficacy analyses were performed to assess the respective relationships in pJIA paediatric subjects treated with the SC regimens in Study WA28117 (n=52). To do so, the steady-state C_{min} computed for each patient was used as the surrogate for exposure.

Logistic regression was used to investigate the exposure-safety relationships between exposure and the safety parameters selected.

Exposure-Efficacy Relationship

As prior TCZ patients were treated with IV TCZ before study start, the exposure-efficacy relationships regarding efficacy measures JADAS-71 and CHAQ-DI scores were investigated only for TCZ naïve patients (n=38). The individual profiles of these measures and percent change from baseline over time were compared for patients by regimen.

JADAS-71:

JADAS-71 decreased over time for both TCZ naive and prior TCZ patients treated with the Q2W and Q3W regimen. Greater decreases in JADAS-71 were observed for TCZ naive patients treated with the Q3W regimen (BW < 30 kg) and with increasing C_{trough} in the naïve patients.

Analogously, when comparing the percent change in JADAS-71 by exposure category for all TCZ naive patients, greater decreases in JADAS-71 across time were observed for patients who were in the highest exposure category with a rather broad range of variability in response across the 3 categories.

CHAQ-DI:

CHAQ-DI scores decreased over time for both TCZ naive and prior TCZ patients treated with the Q2W and Q3W regimen. Similar to JADAS-71, greater decreases in CHAQ-DI scores were observed for patients treated with the Q3W regimen (BW < 30 kg). 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) but the most prominent change in CHAQ-DI score in BW class < 30 kg and C_{trough} below 13 µg/mL. Similar decreases in CHAQ-DI score were observed in both exposure categories for patients treated with the Q2W regimen (BW ≥ 30 kg). When comparing the percent change in CHAQ-DI score by exposure category for all TCZ naive patients, the trends in CHAQ-DI scores across time observed across the 3 exposure categories were comparable. There was no clear relationship between steady-state C_{min} and percent change in CHAQ-DI scores from baseline to Week 52.

Exposure-Safety Relationship

SAE, any AE, and AEs in the Infections and Infestations SOC, which is the most common SOC for pJIA pediatric patients as well as Occurrence of neutropenia AEs and CTC Grade ≥ 3 low neutrophil count laboratory abnormalities have been investigated.

SAE:

A total of 3 patients (5.8%) experienced 4 SAEs during the study. Of the 3 patients who experienced SAEs, one patient was in the <30 kg BW group treated with the Q3W regimen; 2 SAEs were reported for this patient. The other two patients were in the ≥ 30 kg BW group treated with the Q2W regimen. Each of them experienced one SAE. One patient had a Grade 2 decreased appetite SAE and another had a Grade 3 arthralgia SAE. Both of these SAEs required hospitalization; however, neither of those SAEs was considered by the investigator to be related to TCZ SC treatment.

The one patient in the < 30 kg BW group treated with the Q3W regimen experienced 2 SAEs, both of which were considered by the investigator to be related to TCZ SC treatment. This patient had a Grade 4 croup infectious SAE, and this SAE was resolved. One patient experienced a Grade 3 varicella SAE.

Neutropenia AEs and Low Neutrophil Count Laboratory Abnormalities:

Overall, 5 patients (~10%) experienced 11 neutropenia AEs during the SC study. Four of the 5 patients experiencing neutropenia AEs were treated with the 162 mg Q3W regimen (BW < 30 kg), and all 5 patients were naive to TCZ. Of those 5 patients who experienced neutropenia AEs, 3 patients experienced Grade 3 or above neutropenia, and all 3 patients were treated with the 162 mg Q3W regimen (BW < 30 kg).

Based on results of the logistic regression analyses, there is a relationship between TCZ exposure and neutropenia AEs of any grade (see below) with large 90% confidence interval for the regression line. This trend was not statistically significant (p = 0.133) for Grade ≥ 3 neutropenia AEs.

A total of 8 patients experienced CTC Grade 3 low neutrophil count laboratory abnormalities; no patients experienced a Grade 4 or 5 low neutrophil count laboratory abnormality. One of the 8 patients

experiencing Grade 3 low neutrophil count was treated with the 162 mg Q2W regimen (BW ≥ 30 kg), while the other 7 patients were treated with the 162 mg Q3W regimen (BW < 30 kg).

Results from the logistic regression analyses showed that there is a relationship between TCZ exposure and CTC Grade 3 low neutrophil count laboratory abnormalities again with a large 90% confidence interval for the regression line. There were no serious infections associated with Grade 3 low neutrophil counts in Study WA28117.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

PK and PD data has been collected from two clinical studies in the clinical development program for TCZ in pJIA. The clinical PK of TCZ was characterized using the population PK approach which includes 237 paediatric pJIA patients from Studies WA28117 (JIGSAW 117, n = 52) and WA19977 (Cherish, n = 188) resulting in a total PK data set of 3484 serum samples for population PK analyses. From those samples, 831 PK samples have been collected from 52 patients of Study WA28117, who have been treated with either 162 mg of TCZ every 3 weeks (Q3W, children weighing < 30 kg) or 162 mg of TCZ every 2 weeks (Q2W, children ≥ 30 kg). This dosing regimen has been derived by bridging from IV WA19977 study results. As a pivotal first step of bridging, a population PK model has been established on the basis of IV PK data collected from Study WA19977 (N=188, 2653 samples). By combining the population PK model developed for the IV formulation along with prior knowledge on the SC absorption obtained from the adult RA population, PK profiles for different SC dose regimens were simulated for pJIA patients.

The derived final population PK model integrated 3484 PK samples following SC and IV TCZ treatment of pJIA patients. A two-compartment PK model with parallel linear and Michaelis-Menten eliminations, and first-order absorption to describe SC administration was selected to describe the PK of TCZ. The structural model used to describe the PK of TCZ for pJIA was adopted from the model used to describe the PK of TCZ in adult RA patients. 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, VM, and Ka.

After the covariate selection process, the final PK estimates have been calculated indicating a clearance of 0.50 L/day, and a limited volume of distribution of 4 L. Non-linear clearance is characterized by Vm = 5.81 mg/L/day and Km = 0.462μg/mL. The simulated median effective half-life of TCZ during an inter-dose interval at steady-state ranged from 3.5 to 10.3 days (162 Q3W regimen, < 30kg) and from 3.1 to 7.1 days (162 mg Q2W regimen).

The bioavailability estimated for a typical pJIA patient with a BMI of 18 is 96.4%, which is higher compared to that estimated for adult RA patients (79.5%). This can be explained by the BMI-related influence on F and Ka. Within the studied paediatrics population, the covariate effect of BMI especially on Ka was found to be very pronounced (+84%, -60%) at the 2.5th (13 kg/m2) and 97.5th (29.4 kg/m2) percentile of BMI (reference 18 kg/m2).

All model parameters were estimated with an acceptable precision and moderate inter-individual variability. Model parameters are overall comparable between the joint and the IV population PK model. KM and Vm values were slightly lower compared to those derived for the IV population PK model.

Goodness-of-fit plots showed no major abnormalities. However, comparison of individual predictions from the final model with observations, stratified by route of administration and weight groups, match only moderately well. VPC plots showed that for the SC case, the derived PK model underestimates the observed TCZ levels and only meet the 90th percentile of TCZ in the higher body weight group SC acceptably well and the model building process was prone to overfitting. Thus, derived quantitative

conclusions based on the final population PK model regarding exposure-response should be drawn with caution.

Using the individual Bayesian post hoc parameters estimated by the final popPK model, concentration-time profiles were simulated for all pJIA patients and compared following SC und IV treatment, respectively. The median SC TCZ concentration profiles were higher for patients weighing < 30 kg compared to those weighing ≥ 30 kg. For TCZ naive patients, the observed median C_{min} (range) was 20.0 (3.4 - 55.6) µg/mL at Week 12 and 18.6 (3.0-55.9) mg/mL at Week 36 for the <30 kg BW group, and 12.1 (0.6-24.5) µg/mL and 8.8 (0.3-44.1) µg/mL for the ≥ 30 kg BW group, respectively. For prior TCZ patients, the observed median C_{min} (range) was 14.6 (13.2-25.9) µg/mL at Week 12 and 18.3 (4.3-25.1) µg/mL at Week 36 for the < 30 kg BW group and 12.4 (0.4-28.3) µg/mL and 15.8 (3.3-25.0) µg/mL for the ≥ 30 kg BW group, respectively.

Range and height of the driving PK measure C_{trough} in steady state (C_{min_ss}) differed when comparing the IV and SC dosing regimen within both body weight groups (< 30 kg, ≥30 kg). In contrast to the IV regimen, the steady-state C_{min}, C_{max}, $AUC_{12weeks}$, and C_{mean} achieved for patients in the <30 kg BW group were higher compared to the ≥ 30 kg BW group. For pJIA patients with BW ≥30 kg, the AUCss,0-12weeks achieved by the 162 mg SC Q2W regimen was lower compared to that achieved by the 8 mg/kg and 10 mg/kg IV Q4W regimen but mean C_{min_ss} was higher. Due to the flat dosing regimen and the strong BW influence on TCZ PK, children weighing < 10 kg reach comparatively high TCZ levels. Especially in the body weight group <30 kg, mean and median C_{min_ss} (SC) are 12- and 38-fold higher compared to the respective C_{min_ss} mean and median values IV within the respective body weight group.

On the other hand, paediatric subjects at higher body weight achieve lower exposure compared to the body weight adjusted IV regimen.

In comparison with adult RA patients, C_{min} exposures in both pJIA BW groups were within the range of exposures achieved with TCZ SC in adult RA patients. However, the adult exposure range is characterized by a very large variability.

The accumulation ratios for C_{trough} are 3.58 and 2.08 for TCZ 162 mg Q2W and Q3W SC regimens, respectively; for AUC_{tau} and average concentration over the dosing interval (C_{mean}), these ratios are 2.04 and 1.46, respectively. Approximately 90% of the steady-state exposure levels were reached after the 6th SC injection in Q2W regimen, and after the 4th SC injection in Q3W regimen.

Body size related covariates (HT, BSA, and BMI) are detected to be a major source of variability among the paediatric population (IV and SC population) by stepwise covariate selection procedure and is also known from previous authorization procedures. The strong impact became apparent on different kinetic parameters (CL, V, Ka, F). VM rate constant was affected by serum creatinine levels (26% higher and 16% lower at the extreme SCRT values in the data set of 18 and 82 µmol/L respectively, compared to SCRT of 43 µmol/L). Gender had minor effect on VC, VP, and VM parameters (for males, 9% higher VC, and 17% higher VP and VM).

Overall, the 2-compartment model describes the data following IV or SC treatment moderately well.

Pharmacodynamics and PK/PD

The antibody TCZ binds specifically to both sIL-6R and membrane-bound IL-6R to inhibit IL-6R-mediated signalling. Soluble IL-6R, IL-6, C - reactive protein (CRP), erythrocyte sedimentation rate (ESR) have been used as PD biomarker. Overall, PD marker response following IV or SC dosing was comparable over the body weight range with a slightly more pronounced response in patients weighing < 30 kg.

5.8% of the paediatric patients (3 TCZ naïve patients of 52) developed treatment-emergent ADA with neutralizing potential. No apparent effect of ADA on TCZ PK could be detected by population PK analysis; however this may also be due to the sparse data available and included.

In comparison, in the TCZ IV Study WA19977 only 1/185 (0.5%) patients in the TCZ IV Week 40 safety population developed treatment-emergent ADA post-baseline and 2/41 (4.9%) patients (both ≥ 30 kg BW group) in LTE Study WA29231.

As prior TCZ patients were treated with IV TCZ before study start, the exposure-efficacy relationships regarding efficacy measures JADAS-71 and CHAQ-DI scores were investigated only for TCZ naïve patients (n=38). Overall, no clear exposure response relationships with regard to CHAQ-DI Score and JADAS-71 could be detected. However, patients with BW < 30 kg and with C_{trough} in steady state < 13 µg/mL seem to gain the most benefit from treatment, following the efficacy parameters CHAQ-DI Score and JADAS-71.

Regarding exposure safety-relationship, SAE, any AE, and AEs in the Infections and Infestations SOC, which is the most common SOC for pJIA paediatric patients as well as occurrence of neutropenia AEs and CTC Grade ≥3 low neutrophil count laboratory abnormalities have been investigated (n=52). Overall, data and analyses showed a slight exposure response relationship regarding safety with more adverse events and lower blood cell counts in especially the very light patients. According to the applicant, this trend is not clinically relevant. The applicant argues that confidence intervals (from C_{min_ss} of 30 µg/mL onwards) evidencing this relationships are rather large. However, this is due to the small sample size and the relative rarity of these events rather than a sign for clinically non-relevant effects.

The MAH was requested to further elaborate and summarized the relevant safety and efficacy data, and concluded that conducted analyses indicated no correlation between higher TCZ exposures in the lower BW patients and any safety concerns, or between lower TCZ exposures and poorer efficacy outcomes in the higher BW patients. The CHMP concluded that although there were limited numbers of patients in the two body weight extremes, trends but no clear correlation between TCZ exposure-response relationships could be detected that manifest a clinically significant safety or efficacy concern associated with the extremes of body weight. In some patients factors other than weight alone may contribute to poor responses or safety concerns; however the strong body weight related influence on PK should be considered (see section 5.2. of the SmPC).

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data submitted in support of this application is considered acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was conducted. Steady-state C_{min} has been established as the primary PK driver of efficacy for bridging between indications and formulations for TCZ. TCZ SC regimens for adult RA and TCZ IV regimens for pJIA and sJIA based on steady-state C_{min} have been proposed previously using modelling and simulation, which were validated in the adult RA SC and pJIA and sJIA IV programs leading to approval.

In the pJIA IV program, the optimal dosing regimen of TCZ IV was 10 mg/kg Q4W in patients weighing < 30 kg and 8 mg/kg Q4W in patients weighing ≥ 30 kg. In order to

allow for SC delivery of TCZ in pJIA, a dosing strategy was developed using the adult SC formulation (1-mL PFS + NSD delivering 162 mg of TCZ in 0.9 mL), which would provide an efficacious range of exposures across the wide range of BWs encountered in paediatric patients.

Based on the population PK model developed for the pJIA IV formulation along with prior knowledge on the SC absorption obtained from the adult RA population, PK profiles for different SC dose regimens were simulated for pJIA patients, with a focus on the steady-state C_{min} (primary PK driver of efficacy). Based on the simulation results, the Q2W (BW ≥ 30 kg) and Q3W (BW < 30 kg) TCZ SC regimens were recommended for pJIA patients because most of the patients were predicted to achieve a steady-state C_{min} above the 5th percentile of that achieved by the TCZ IV formulation, across the body weight spectrum for pJIA patients.

2.4.2. Main study

Study WA28117 – A Phase Ib, Open-Label, Multicentre Study to Investigate the Pharmacokinetics, Pharmacodynamics, and Safety of Tocilizumab following Subcutaneous Administration to Patients with Polyarticular Juvenile Idiopathic Arthritis

Methods

Figure 10 - Overview of TCZ SC WA28117 Study Design
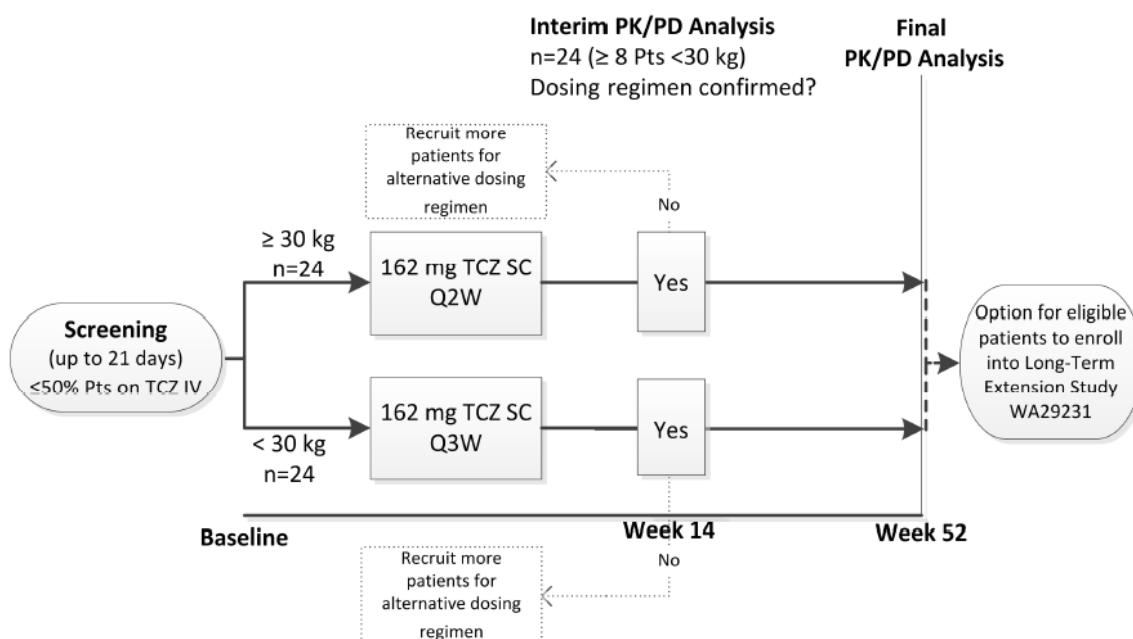
Study participants

Children aged 1 year (12 years for patients in Russia) up to and including 17 years old with active pJIA (according to ILAR classification: RF-positive pJIA, RF-negative pJIA or eoJIA with a polyarticular course) with an inadequate response to or inability to tolerate methotrexate (MTX), who were receiving standard of care, either with or without non-steroidal anti-inflammatory drugs (NSAIDs), either with or without oral corticosteroids, and either with or without concomitant MTX therapy including patients with well-controlled disease receiving current treatment with TCZ IV (including patients who participated in Study WA19977) and TCZ-naive patients with active disease, were eligible for inclusion in the study. The total number of patients switching from TCZ IV must have accounted for no more than 50% of the total subject number (i.e., n ≤ 24).

Patients receiving TCZ IV 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.

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: TCZ SC every 3 weeks (Q3W)

- Patients weighing ≥ 30 kg: TCZ SC Q2W every 2 weeks (Q2W)

For patients switching from TCZ IV to TCZ SC at baseline and who had well-controlled disease did not require a period of discontinuation of TCZ IV and should have had their first dose of TCZ SC administered on the date that their next TCZ IV infusion would had been due.

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

Objectives

- Pharmacokinetic (PK) Objective: to characterize the pharmacokinetics of TCZ SC in patients with pJIA

- Pharmacodynamic (PD) Objective: to evaluate the pharmacodynamics of TCZ SC in patients with pJIA

- Safety Objective: evaluate the safety of TCZ SC in patients with pJIA

- Exploratory Objective: to describe the efficacy of TCZ SC in patients with pJIA

Outcomes/endpoints

Pharmacokinetics

Serum TCZ concentration and population PK model-predicted PK exposures (AUC, maximum concentration [C_{max}], and C_{min}) for the Q2W and Q3W dosing regimens at steady state

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)

Sample size

Based on the methodology proposed in Wang et al. (2012) on determining sample size for paediatric PK studies, a sample size of approximately 48 patients (24 per weight group and no more than 50% IV switchers in total) was estimated to achieve a probability (power) of at least 80% to have the 95% confidence interval 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 WA19977. These results were obtained from 1000 simulations of trials with 48 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 pcJIA. A sample size of 48 patients completing the study should ensure a 95% probability of observing at least one AE for which the underlying incidence of that event is ≥ 6.1%, however, safety considerations were not considered of relevance for planning the sample size of this study.

Randomisation

WA28117 was a single-arm study. Patients were assigned to one of two dose groups based on bodyweight (< 30 kg: 162 mg of SC TCZ Q3W, ≥ 30 kg: 162 mg of SC TCZ Q2W).

Blinding (masking)

Open label study.

Statistical methods

Objectives in study WA28117 (Jigsaw 117) 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.

Three analysis sets were defined: the PK/PD analysis set (PP set with sufficient PK/PD data; excluded cases were to be documented together with the reason for exclusion), the ITT set (all enrolled patients with at least one dose of TCZ SC), and the safety set (ITT set with at least one safety assessment, analysed as treated).

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

Absolute and change from baseline values for JADAS-71 data are summarized by patient TCZ status, "TCZ Naive" or "Prior TCZ", or by TCZ status for each BW category, and for "All Patients" by visit.

Results

Participant flow

Of the 61 patients screened, a total of 52 patients were enrolled into this study and received TCZ.

Figure 11 - Patient disposition
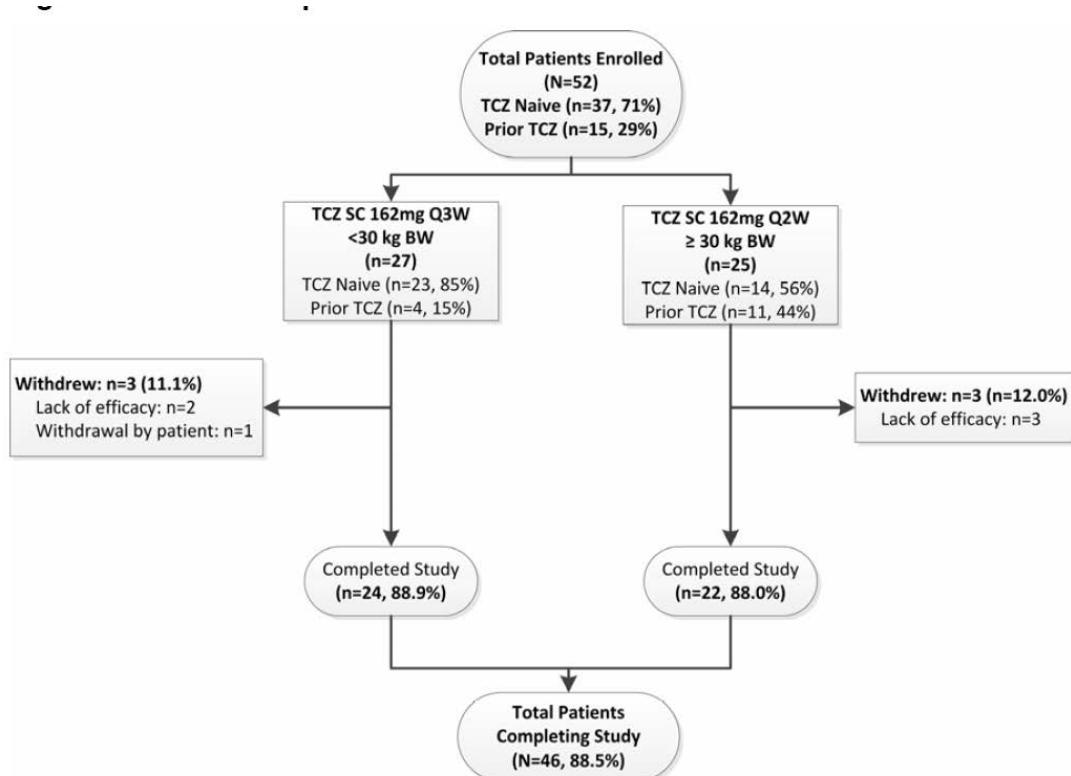
Of the 61 patients screened, a total of 52 patients were enrolled into this study and received TCZ. The most common reasons for screening failure were 'met exclusion criteria' and 'withdrew consent'.

Patients received open-label TCZ SC treatment based on BW, with 27 patients weighing < 30 kg receiving

162 mg of TCZ Q3W and 25 patients weighing ≥ 30 kg receiving 162 mg of TCZ Q2W. Of these 52 patients, 37 (71%) were naive to TCZ at baseline and 15 (29%) were receiving TCZ IV before entering the study. The ≥ 30 kg BW group had a higher proportion (44%) of patients with prior TCZ experience compared with the < 30 kg BW group (15%).

Conduct of the study

There were 2 global and one country specific study protocol amendments (Amendment 3, Russia only).

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

Four patients had protocol violations, none of which were considered significant enough to exclude them from the PK/PD population; all of these patients completed the study. Three of the 4 patients had exclusion criteria violations: 1 patient with tuberculosis, 1 patient with incomplete/missing exclusion criteria, and 1 patient with neutrophil and WBC counts below the exclusion criteria minimum. The other protocol violations were procedural.

Protocol Amendment, Version 4 (1 August 2013)

• To limit the number of patients switching from TCZ IV to TCZ SC was limited to no more than 50% of the total number of subjects, and to include the a request was included to collect information on the prior four IV infusions for patients switching from TC IV to TCZ SC.

Changes to Planned Analyses

It is stated that there were no changes to the planned analyses as originally specified in the SAP that significantly affected or altered the analysis of safety or efficacy data. However, it should be noted that the SAP defined the efficacy measure of "inactive disease" to include the criterion "duration of morning stiffness ≤ 15 minutes". This criterion was not used in the analysis of inactive disease for this study because the "inactive disease" analysis reported in Study WA19977 (TCZ IV in patients with pJIA) also did not use it.

Baseline data

The 52 patients enrolled into the study were predominantly female and Caucasian. The median age and height were all higher in the ≥ 30 kg BW group compared with the < 30 kg BW group, which was as expected for these BW dosing groups.

Though patient numbers are small, the baseline disease characteristics were generally comparable between the two BW groups. The median JADAS-71 and CHAQ-DI scores were comparable between the two BW groups (< 30 kg: 16.2 and 0.75 vs. ≥ 30 kg: 15.0 and 0.50). Additionally, there were no meaningful differences in the core components of the JADAS-71 (physician's and patient/parent's global assessment VAS, number of active joints, and ESR) between the two BW groups. As expected, patients

who were naive to TCZ (n=37) had higher JADAS-71 and CHAQ-DI scores, and a higher number of active joints compared with patients with prior TCZ experience (n=15).

The proportion of patients on background oral corticosteroids at baseline was comparable between the two BW groups (< 30 kg: 40.7% vs. ≥ 30 kg: 48.0%). All patients in the study had previous non-biologic disease-modifying anti-rheumatic drug (DMARD) use (including MTX); however, a higher proportion of previous biologic DMARD use was seen in the ≥ 30 kg BW group compared with the < 30 kg group (84.0% vs. 37.0%, respectively), and a higher proportion of background MTX use occurred in the < 30 kg BW group compared with the ≥ 30 kg BW group (77.8% vs. 60.0%, respectively).

Tumour necrosis factor (TNF) antagonists were not permitted during the study but were previously used by 15.4% of patients; previous use was comparable between the two BW groups (< 30 kg: 18.5% vs. ≥ 30 kg: 12.0%).

Table 6 - Key demographics and disease characteristics at baseline for WA28117

	TCZ SC (WA28117)			
	TCZ SC Q3W (< 30 kg) N = 27		TCZ SC Q2W (≥ 30 kg) N = 25	
	TCZ Naive (n=23)	Prior TCZ (n=4)	TCZ Naive (n=14)	Prior TCZ (n=11)
Age (years), mean (SD)	5.3 (2.1)	6.8 (1.0)	14.9 (2.2)	12.7 (2.9)
Min – Max	1[a] – 9	6 – 8	11 – 17	7 – 16
Females, n (%)	14 (61%)	4 (100%)	10 (71%)	8 (73%)
Weight (kg), mean (SD)	19.21 (4.934)	22.20 (1.283)	60.35 (15.128)	51.96 (15.251)
Min – Max	12.00 – 28.00	20.50 – 23.60	34.20 – 97.90	34.40 – 82.00
Prior non-biologic DMARD use [b], n (%)	23 (100%)	4 (100%)	14 (100%)	11 (100%)
Prior biologic DMARD use, n (%)	6 (26%)	4 (100%)	10 (71%)	11 (100%)
Background oral CS use, n (%)	11 (48%)	0 (0.0%)	6 (43%)	6 (55%)
Background MTX use, n (%)	18 (78%)	3 (75%)	7 (50%)	8 (73%)
ESR (mm/hr), mean (SD)	17.7 (14.7)	5.5 (2.1)	15.9 (13.4)	9.2 (12.3)
C-Reactive Protein (mg/L), mean (SD)	3.944 (5.538)	0.210 (0.020)	5.491 (8.741)	0.638 (0.832)
JADAS-71 (0-101), median (Min – Max)	18.10 (1.9 – 40.4)	3.90 (0.0 – 15.7)	20.05 (9.4 – 48.2)	6.90 (0.0 – 44.4)
CHAQ-DI Score (0-3), mean (SD)	0.95 (0.662)	0.50 (0.510)	0.88 (0.701)	0.59 (0.733)

Numbers analysed

All 52 patients enrolled received at least one dose of treatment (i.e., 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. Additionally, no patients took the growth hormone somatropin during the study, meaning all the growth analyses also use the safety population

Table 7 - Summary of analysis population

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Analysis Populations, All Patients Population
Protocol: WA28117
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	TCZ SC 162 mg Q3W (< 30 kg) (N=27)	TCZ SC 162 mg Q2W (>= 30 kg) (N=25)	All TCZ (N=52)
Safety Population	27	25	52
Total Exclusions	0	0	0
ITT Population	27	25	52
Total Exclusions	0	0	0
PK/PD Population	27	25	52
Total Exclusions	0	0	0

```
Program: /opt/BIOSTAT/prod/cn11935c/i28117b/t_pop.sas / Output:
/opt/BIOSTAT/prod/cn11935c/i28117b/reports/t_pop_AP.out
28JUL2016 11:03                                      Page 1 of 1
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Outcomes and estimation

The efficacy results for TCZ SC Study WA28117 are exploratory in nature as the study was not controlled, and only 37 of the 52 patients were TCZ naive, in whom the efficacy evaluation is most informative. JADAS-71 was used as the key efficacy endpoint measure in the study.

Table 8 - Summary of key efficacy results from TCZ SC WA28117

	TCZ SC (WA28117)								
	162 mg Q3W (< 30 kg)			162 mg Q2W (≥ 30 kg)					
	TCZ Naive (n = 23)	Prior TCZ (n = 4)	All Patients (n = 27)	TCZ Naive (n = 14)	Prior TCZ (n = 11)	All Patients (n = 25)	All TCZ Naive (n = 37)	All Prior TCZ (n = 15)	All TCZ SC (N = 52)
JADAS-71 median									
Baseline	18.10	3.90	16.20	20.05	6.90	15.00	19.60	6.20	15.95
(Min − Max)	(1.9 − 40.4)	(0.0 − 15.7)	(0.0 − 40.4)	(9.4 − 48.2)	(0.0 − 44.4)	(0.0 − 48.2)	(1.9 − 48.2)	(0.0 − 44.4)	(0.0 − 48.2)
Week 51/52	0.30	0.30	0.30	3.00	1.10	2.05	1.20	0.65	0.90
(Min − Max)	(0.0 − 24.5)	(0.0 − 2.6)	(0.0 − 24.5)	(0.1 − 20.4)	(0.0 − 27.6)	(0.0 − 27.6)	(0.0 − 24.5)	(0.0 − 27.6)	(0.0 − 27.6)
Pain VAS mean (± SD)									
Baseline	41.1 (30.9)	19.0 (14.8)	37.8 (29.9)	47.9 (24.8)	25.5 (28.9)	38.1 (28.4)	43.7 (28.6)	23.8 (25.6)	37.9 (28.9)
Week 51/52	9.9 (15.6)	3.0 (5.4)	8.8 (14.6)	19.8 (19.0)	13.9 (19.8)	17.1 (19.1)	13.5 (17.3)	10.8 (17.4)	12.7 (17.2)
Inactive Disease									
Baseline	0/23 (0.0%)	2/4 (50.0%)	not calculated	0/14 (0.0%)	4/11 (36.4%)	not calculated	0/37 (0.0%)	6/15 (40.0%)	6/52 (11.5%)
Week 51/52	17/21 (81.0%)	3/4 (75.0%)	not calculated	7/12 (58.3%)	6/10 (60.0%)	not calculated	24/33 (72.7%)	9/14 (64.3%)	33/47 (70.2%)
Clinical Remission									
Week 36	4/22 (18.2%)	2/4 (50.0%)	not calculated	0/12 (0.0%)	1/10 (10.0%)	not calculated	4/34 (11.8%)	3/14 (21.4%)	7/48 (14.6%)
Week 51/52	8/21 (38.1%)	3/4 (75.0%)	not calculated	2/12 (16.7%)	3/10 (30.0%)	not calculated	10/33 (30.3%)	6/14 (42.9%)	16/47 (34.0%)
CHAQ-DI mean (± SD)									
Baseline	0.95 (0.66)	0.50 (0.51)	0.88 (0.65)	0.88 (0.70)	0.59 (0.73)	0.76 (0.72)	0.93 (0.67)	0.57 (0.66)	0.82 (0.68)
Week 51/52	0.26 (0.43)	0.00 (0.00)	0.22 (0.40)	0.71 (0.95)	0.30 (0.52)	0.52 (0.79)	0.42 (0.68)	0.2143 (0.45)	0.36 (0.63)

Sources:
WA28117 CSR: t_ef_SE_JADAS_C, t_ef_SE_PTPAIN_C, t_ef_prop_SE_INACT, t_ef_prop_SE_REMIS, t_ef_SE_CHAQ_C.

SCE: SPAAH169_t_ef_SE_JADAS_C, SPAAH169_t_ef_SE_PTPAIN_C, SPAAH169_t_ef_prop_SE_INACT, SPAAH169_t_ef_prop_SE_REMIS, SPAAH169_t_ef_SE_CHAQ_C.

In the TCZ naive patients weighing < 30 kg (n=23), the median JADAS-71 reduced to the level of inactive disease (< 1.0) by Week 27, and generally remained at this level for rest of study. In the TCZ naive patients weighing ≥ 30 kg (n=14), the median JADAS-71 dropped to near minimal disease activity (< 3.8) by Week 20 and remained essentially at this level throughout the rest of the study.

Growth

No patients took the growth hormone somatotropin during the study. The growth analyses were performed using the safety population. Overall normal growth patterns were observed in Study WA28117.

Patients displayed an expected distribution of height velocities during the study. A plot of 1 year height velocity against WHO expected 1 year height velocity confirms a generally normal pattern of growth in patients during the study period (data not shown in his report). There was no difference between the TCZ naive and prior TCZ patients.

Supportive studies

Study WA19977

Study WA19977 was a 24 week randomised double-blind, placebo controlled withdrawal trial (Part II) with a 16 week open-label lead-in phase (Part I), and 64-week open-label follow-up (Part III) to evaluate the efficacy and safety of tocilizumab in patients with active polyarticular juvenile idiopathic arthritis.

The study consisted of three parts:

- Part I was a 16-week open-label TCZ IV treatment lead-in period.

- Part II was a 24-week randomized, double-blind, placebo-controlled withdrawal period in which patients were randomized to treatment with TCZ IV (at the same dose as in Part I) or to placebo.

- Part III was a 64-week open-label period beginning at Week 40 to examine the effect of long-term use of TCZ IV on safety and efficacy.

Figure 12 - Overview study design
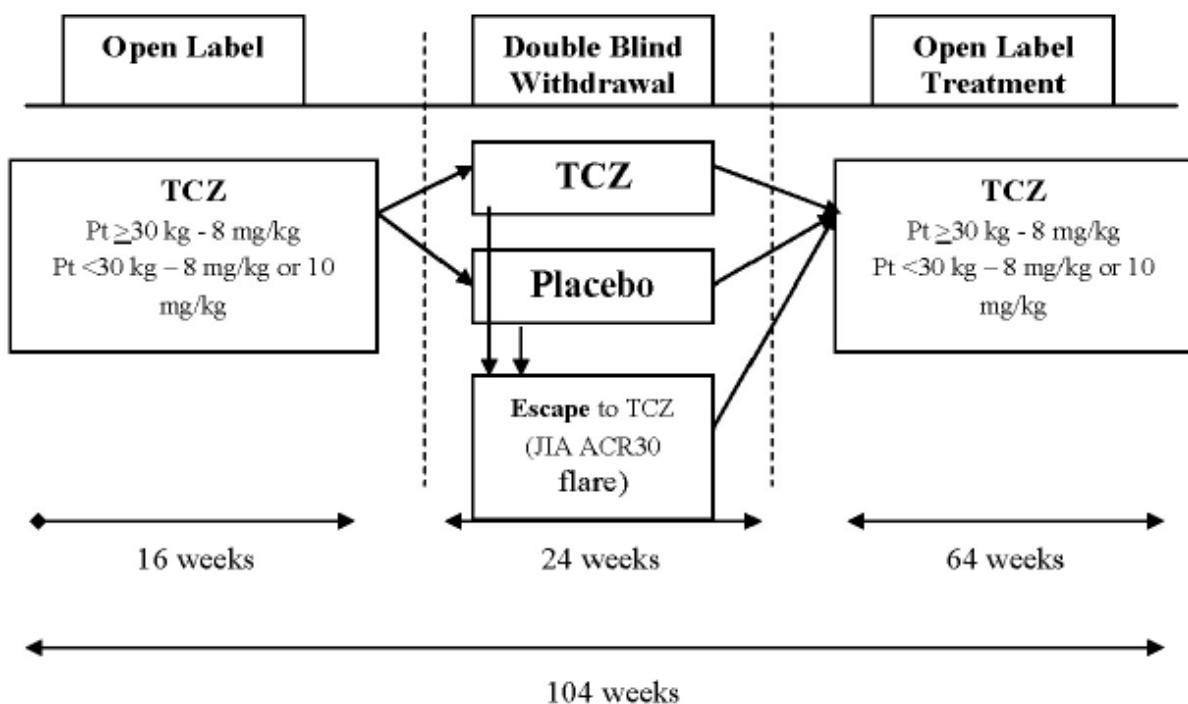
The target patient population of study WA19977 was patients of 2 to 17 years of age with documented evidence for at least 6 months prior to study entry of RF-positive or RF negative pJIA or of extended oligoarticular arthritis according to ILAR criteria. Disease had to be active at screening and baseline with at least five joints with active arthritis (joints that were swollen or if no swelling was present limitation of movement accompanied by pain, tenderness or both), with at least 3 of the active joints having limitation of motion. The patients also had to have had an inadequate response to methotrexate (MTX) or inability to tolerate MTX. Patients previously treated with any cell depleting therapy, including any investigational agents (e.g. anti-CD19 and anti-CD20) were not permitted in the study.

Treatment

Part I: Active treatment lead-in period, every 4 weeks for 4 doses. The total duration was 16 weeks with dosing at baseline, Weeks 4, 8 and 12.

- < 30 kg randomized 1:1 to either TCZ 8 mg/kg or 10 mg/kg intravenous (IV) infusion

- ≥ 30 kg TCZ 8 mg/kg IV infusion

Part II: Double-blind withdrawal period. All subjects were randomized to either

- TCZ (at the same dose as Part I)

- Placebo

This withdrawal period lasted from Week 16 through Week 40 with the last dose at Week 36.

Part III: Open-Label (Part I dose resumed).

Study WA29231

WA29231 study population consists of patients who have completed Study WA28117 or Study WA28118 study, and had an adequate response to TCZ SC therapy. The efficacy objective for Study WA29231 is to assess the long-term efficacy of TCZ SC in patients with pJIA and sJIA. In this report, only the data from pJIA patients are presented. At the time of the clinical cut-off (17 July 2016), 41 patients who completed

Study WA28117 had enrolled in Study WA29231. Among those patients, 5 patients completed clinical assessments and had data available at Week 12, 36, 60, 84 and 96, respectively.

Results

Baseline disease characteristic and previous concomitant medication

Table 9 - Key demographics and disease characteristics at baseline for WA28117, WA19977 and WA29231

| | TCZ SC (WA28117) | | | | TCZ IV (WA19977) | | TCZ SC LTE (WA29231) | |
| | TCZ SC Q3W (< 30 kg) N = 27 | | TCZ SC Q2W (≥ 30 kg) N = 25 | | 10 mg/kg Q4W (< 30 kg) N = 22 | 8 mg/kg Q4W (≥ 30 kg) N = 119 | TCZ SC Q3W (< 30 kg) N = 21 | TCZ SC Q2W (≥ 30 kg) N = 20 |
	TCZ Naive (n=23)	Prior TCZ (n=4)	TCZ Naive (n=14)	Prior TCZ (n=11)				
Age (years), mean (SD)	5.3 (2.1)	6.8 (1.0)	14.9 (2.2)	12.7 (2.9)	6.9 (3.02)	13.1 (2.8)	6.6 (2.1)	14.7 (2.8)
Min – Max	1ᵃ – 9	6 – 8	11 – 17	7 – 16	2 – 11	6 – 17	2 – 10	8 – 18
Females, n (%)	14 (61%)	4 (100%)	10 (71%)	8 (73%)	21 (95%)	90 (76%)	16 (76.2%)	14 (70.0%)
Weight (kg), mean (SD)	19.21 (4.934)	22.20 (1.283)	60.35 (15.128)	51.96 (15.251)	17.69 (4.864)	50.02 (12.552)	24.06 (6.41)	59.28 (14.46)
Min – Max	12.00 – 28.00	20.50 – 23.60	34.20 – 97.90	34.40 – 82.00	9.6 – 26.6	30.7 – 85.1	14.8 – 36.8	36.8 – 96.8
Prior non-biologic DMARD use ᵇ, n (%)	23 (100%)	4 (100%)	14 (100%)	11 (100%)	13 (59%)	87 (73%)	20 (95.2%)	20 (100.0%)
Prior biologic DMARD use, n (%)	6 (26%)	4 (100%)	10 (71%)	11 (100%)	5 (23%)	47 (39%)	17 (81.0%)	20 (100.0%)
Background oral CS use, n (%)	11 (48%)	0 (0.0%)	6 (43%)	6 (55%)	7 (32%)	54 (45%)	2 (9.5%)	6 (30.0%)
Background MTX use, n (%)	18 (78%)	3 (75%)	7 (50%)	8 (73%)	17 (77%)	89 (75%)	12 (57.1%)	13 (65.0%)
ESR (mm/hr), mean (SD)	17.7 (14.7)	5.5 (2.1)	15.9 (13.4)	9.2 (12.3)	32.0 (22.4)	34.2 (26.67)	4.0 (3.1)	5.4 (3.4)
C-Reactive Protein (mg/L), mean (SD)	3.944 (5.538)	0.210 (0.020)	5.491 (8.741)	0.638 (0.832)	19.51 (30.20)	22.80 (38.81)	0.341 (0.516)	0.401 (0.459)
JADAS-71 (0-101), median (Min – Max)	18.10 (1.9 – 40.4)	3.90 (0.0 – 15.7)	20.05 (9.4 – 48.2)	6.90 (0.0 – 44.4)	36.23 (10.1 – 77.2)	28.49 (11.1 – 88.5)	0.70 0.0 – 18.4	2.05 0.0 – 27.6
CHAQ-DI Score (0-3), mean (SD)	0.95 (0.662)	0.50 (0.510)	0.88 (0.701)	0.59 (0.733)	1.69 (0.711)	1.20 (0.690)	0.211 (0.425)	0.488 (0.773)

CHAQ-DI = Childhood Health Assessment Questionnaire Disability Index; CS = corticosteroid; DMARD = Disease-Modifying Anti-Rheumatic Drug; ESR = Erythrocyte sedimentation rate; IV = intravenous; JADAS-71 = Juvenile Arthritis Disease Activity Score 71; MTX = methotrexate; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab; VAS = Visual Analog Scale.

Note: The most directly comparable treatment groups from Study WA28117 and Study WA19977 are highlighted with matching colors.

ᵃ One patient < 2 years old (aged 1 year 11 months at baseline) was recruited into the study.

ᵇ MTX is included in prior non-biologic DMARD use for Study WA28117 and LTE Study WA29231 but excluded for Study WA19977.

Sources: WA28117 CSR, Table 4; 104-Week WA19977 CSR:, Table 4 and stdm11_gdcb_i; LTE WA29231: t_dm_SE

Baseline disease characteristics and previous or concomitant medication use in the TCZ SC Study WA28117 (i.e., TCZ naive SC patients) were generally comparable with those in the TCZ IV Study WA19977, with the following notable differences: a higher proportion of patients weighing ≥ 30 kg received prior biologic DMARDs in the TCZ SC study (TCZ naive SC, 71%) compared with patients weighing ≥ 30 kg in the TCZ IV study (39%), and the TCZ SC study patients had lower disease activity and better physical function at baseline, as measured by median JADAS-71 and mean CHAQ-DI scores compared with the TCZ IV study patients.

Patients in the LTE Study WA29231 had lower disease activity (JADAS-71) and better physical function (CHAQ-DI) compared with the prior TCZ patients in WA28117, indicating overall improvement or maintenance of efficacy in the patients enrolling from WA28117 who received an additional year or more of TCZ therapy.

Efficacy

In the TCZ IV Study WA19977, all patients enrolled were TCZ naive per protocol, whereas in the TCZ SC Study WA28117, 15 out of 52 patients overall (29%) were receiving TCZ IV (denoted 'Prior TCZ') before enrolling into the study. Per the WA28117 protocol, up to 50% of patients previously on commercial TCZ IV could be enrolled if their disease was well controlled; these patients then switched to TCZ SC.

Therefore, the 'TCZ naive' BW dosing groups in the TCZ SC WA28117 study are more directly comparable to the TCZ IV WA19977 study population for efficacy results.

Previously in the TCZ IV Study WA19977, the JIA American College of Rheumatology (ACR) response, specifically JIA ACR30 flare, was used as the primary efficacy endpoint measure. The main efficacy comparison between the TCZ SC Study WA28117 and TCZ IV Study WA19977 detailed in this section is based on JADAS-71, which was collected in both studies.

The main focus is on TCZ SC efficacy data from the TCZ naïve patients (n = 37) through Week 52 from Study WA28117 compared with TCZ IV efficacy data from the "continuous TCZ" IV subgroup (n = 82) through Week 52 from Study WA19977.

Table 10 - Comparison of TCZ SC (WA28117) and TCZ IV (WA19977) JADAS-71

	TCZ Naive SC (WA28117)			Continuous TCZ IV (WA19977)		
	162 mg Q3W (< 30 kg)	162 mg Q2W (≥ 30 kg)	All	10 mg/kg Q4W < 30 kg	8 mg/kg Q4W≥ 30 kg	All [a]
	n = 23	n = 14	n = 37	n = 9	n = 55	n=82
Baseline	n = 23	n = 14	n = 37	n = 9	n = 54	n = 81
median JADAS-71	18.10	20.05	19.60	34.00	27.77	28.38
(min – max)	(1.9 – 40.4)	(9.4 – 48.2)	(1.9 – 48.2)	(11.9 – 77.2)	(11.1 – 88.5)	(11.1 – 88.5)
mean (SD)	19.65 (9.78)	21.04 (9.93)	20.18 (9.72)	34.80 (22.92)	31.26 (15.12)	31.43 (15.38)
Week 12	n = 23	n = 14	n = 37	n = 9	n = 55	n = 82
median JADAS-71	5.50	9.75	6.60	4.50	7.00	6.50
(min – max)	(0.0 – 30.1)	(1.9 – 26.8)	(0.0 - 30.1)	(0.5 – 35.7)	(0.0 – 47.5)	(0.0 – 47.5)
mean (SD)	7.59 (8.35)	11.76 (8.20)	9.17 (8.43)	11.59 (13.18)	11.24 (11.94)	11.35 (11.93)
Week 36	n = 22	n = 12	n = 34	n = 8	n = 55	n = 81
median JADAS-71	1.50	4.60	1.75	1.75	2.60	2.60
(min – max)	(0.0 – 23.8)	(0.0 – 21.1)	(0.0 – 23.8)	(0.1 – 47.7)	(0.0 – 51.6)	(0.0 – 51.6)
mean (SD)	3.10 (6.34)	5.95 (5.98)	4.11 (6.28)	8.31 (16.24)	7.11 (11.58)	7.06 (11.19)
Week 51/52	n = 21	n = 12	n = 33	n = 8	n = 54	n = 80
median JADAS-71	0.30	3.00	1.20	0.60	1.60	1.60
(min – max)	(0.0 – 24.5)	(0.1 – 20.4)	(0.0 – 24.5)	(0.0 – 3.1)	(0.0 – 58.4)	(0.0 – 58.4)
mean (SD)	3.01 (6.77)	4.79 (5.70)	3.66 (6.37)	1.13 (1.15)	5.61 (11.38)	5.24 (10.00)

IV – intravenous; JADAS-71 – Juvenile Arthritis Disease Activity Score 71; Q2W – every 2 weeks; Q3W – every 3 weeks; Q4W – every 4 weeks; SC – subcutaneous; TCZ – tocilizumab.
Notes for WA28117: LOCF applied to missing core components at visits.
Notes for WA19977: LOCF applied to missing core components at visits. For all treatment groups presented for WA19977, the 'continuous TCZ IV' patients are shown: this includes only the patients that were randomized to TCZ in Part II of Study WA19977, and therefore received TCZ in all three parts of the study without a break in treatment to receive placebo, as per the withdrawal design. [a] The 'All TCZ' group presented for WA19977 has an n = 82 because it includes all dosing groups within the study: dosing groups 'TCZ 10 mg/kg to TCZ 8 mg/kg (< 30 kg)' n = 7 and 'TCZ 8 mg/kg (< 30 kg)' n = 11 are not shown.
Sources: WA28117:t_ef_SE_JADAS_C; SPAAH169t_ef_SE_JADAS_C; WA19977: etefsum01_j71_v5_tcz_it3_ap123_nwd.

Table 11 - Inactive disease at week 51/52

	TCZ Naive SC (WA28117)			Continuous TCZ IV (WA19977)		
	162 mg Q3W < 30 kg (n = 23)	162 mg Q2W ≥ 30 kg (n = 14)	All (n = 37)	10 mg/kg Q4W < 30 kg (n = 9)	8 mg/kg Q4W ≥ 30 kg (n = 55)	All (n=82)
Inactive Disease (%)	17/23[a] (74.0)	7/14[a] (50.0)	24/37[a] (64.9)	6/9 (66.7)	28/55 (50.9)	43/82 (52.4)

IV = intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.
[a] Data for WA28117 presented with non-responder imputation for patients who withdrew due to non-safety reasons to allow comparison with WA19977.
Source: WA28117:t_ef_prop_SE_INACT; SPAAH169_t_ef_prop_SE_INACT; 104-Week CSR WA19977:etrsfrq02_ind_it3_v6_ap123_tcz.

The proportion of patients with inactive disease at Week 51/52 was numerically higher for the TCZ naive SC versus TCZ IV patients, although the proportions were based on small sample sizes. Overall, 64.9% of

TCZ naive SC patients from WA28117 achieved inactive disease versus 52.4% of TCZ IV patients from WA19977

Table 12 - Clinical remission

	TCZ Naive SC (WA28117)			Continuous TCZ IV (WA19977)		
	162 mg Q3W	162 mg Q2W		10 mg/kg Q4W	8 mg/kg Q4W	
	< 30 kg	≥ 30 kg	All	< 30 kg	≥ 30 kg	All
	n = 23	n = 14	n = 37	n = 9	n = 55	n=82
Clinical Remission (%)	8/23[a] (34.7)	2/14[a] (14.2)	10/37[a] (27.0)	2/9 (22.2)	10/55 (18.2)	15/82 (18.3)

IV = intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] Data for WA28117 presented with non-responder imputation for patients who withdrew due to non-safety reasons to allow comparison with WA19977.

Source: WA28117:t_ef_prop_SE_REMIS; SPAAH169_t_ef_prop_SE_REMIS; 104-Week WA19977 CSR:Table 9.

The proportion of patients who achieved clinical remission at Week 51/52 was numerically higher for TCZ naive SC patients from WA28117 (27.0%) versus TCZ IV patients from WA19977 (18.3%), although the proportions were based on small sample sizes. A higher (numerically) proportion of patients in the < 30 kg BW group achieved clinical remission with TCZ SC versus TCZ IV, whereas the proportion of patients weighing ≥ 30 kg achieving clinical remission was comparable for TCZ SC versus TCZ IV.

Table 13 - Comparison of TCZ SC and TCZ IV CHAQ-DI

	TCZ Naive SC (WA28117)			Continuous TCZ IV (WA19977)		
	162 mg Q3W (< 30 kg)	162 mg Q2W (≥ 30 kg)	All	10 mg/kg Q4W < 30 kg	8 mg/kg Q4W ≥ 30 kg	All
	n = 23	n = 14	n = 37	n = 9	n = 55	n=82
Baseline	23	14	37	9	55	82
Mean CHAQ-DI	0.95	0.89	0.93	1.63	1.08	1.22
SD	0.66	0.70	0.67	0.50	0.68	0.67
Week 12	23	14	37	8	55	81
Mean CHAQ-DI	0.55	0.71	0.61	0.66	0.50	0.60
SD	0.56	0.75	0.63	0.58	0.56	0.57
Week 36	22	12	34	8	54	80
Mean CHAQ-DI	0.28	0.60	0.39	0.58	0.26	0.37
SD	0.42	0.66	0.53	0.53	0.42	0.47
Week 51/52	21	12	33	8	53	79
Mean CHAQ-DI	0.26	0.71	0.42	0.55	0.22	0.32
SD	0.43	0.95	0.68	0.51	0.39	0.48

IV = intravenous; CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index.
IV = intravenous; JADAS-71 = Juvenile Arthritis Disease Activity Score 71; Q2W = every 2 weeks;
Q3W = every 3 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.
Source: WA28117: t_ef_SE_CHAQ_C; SPAAH169_t_ef_SE_CHAQ_C; 104-Week WA19977
CSR: etefsum01_haq_nr_v5_tcz_it3_p123.

Table 14 - Height standard deviation score

	TCZ Naive SC (WA28117)		Continuous TCZ IV (WA19977)	
	162 mg Q3W < 30 kg n = 23	162 mg Q2W ≥ 30 kg n = 14	10 mg/kg Q4W < 30 kg n = 9	8 mg/kg Q4W ≥ 30 kg n = 55
Baseline Mean Height SDS (SD)	−0.24 (1.16)	0.34 (0.81)	−1.03 (1.06)	−0.02 (1.18)
6 Months[a] Mean Height SDS (SD)	−0.22 (1.07)	0.29 (0.81)	−0.68 (1.02)	0.06 (1.15)
1 Year Mean Height SDS (SD)	−0.13 (1.08)	0.39 (0.80)	−0.47 (1.13)	0.09 (1.07)

IV = intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab; TCZ = tocilizumab.

[a] Week 24 data were used for WA19977.

Sources: WA28117 CSR:t_grwth_hv_hsds;

104-Week WA19977 CSR:etgrfrq01_gr_tcz_hsds_rw_wn1_nwd

In both BW groups in both studies, the mean height SDSs were maintained from Baseline to 6 Month and 1 Year, indicating normal growth trajectories.

Long-term extension efficacy data from WA29231

Table 15 - Efficacy results for LTE WA29231

TCZ	JADAS-71 (median) 162 mg Q3W < 30 kg	162 mg Q2W ≥ 30 kg	All	Inactive Disease (%)[a] 162 mg Q3W < 30 kg	162 mg Q2W ≥ 30 kg	All	Clinical Remission (%)[b] 162 mg Q3W < 30 kg	162 mg Q2W ≥ 30 kg	All	CHAQ-DI (mean) 162 mg Q3W < 30 kg	162 mg Q2W ≥ 30 kg	All
Baseline	n = 20 0.70	n = 20 2.05	n = 40 1.25	n = 21 76.2	n = 20 55.0	n = 41 65.9	n = 21 NA	n = 20 NA	n = 41 NA	n = 19 0.21	n = 20 0.49	n = 39 0.35
Week 12	n = 19 0.20	n = 19 0.90	n = 38 0.75	n = 20 70.0	n = 19 68.4	n = 39 69.2	n = 20 NA	n = 19 NA	n = 39 NA	n = 20 0.31	n = 19 0.49	n = 39 0.39
Week 36	n = 13 0.00	n = 18 1.65	n = 31 1.30	n = 13 61.5	n = 18 61.1	n = 31 61.3	n = 13 46.2	n = 18 44.4	n = 31 45.2	n = 13 0.40	n = 16 0.31	n = 29 0.35
Week 60	n = 10 0.40	n = 14 2.30	n = 24 1.75	n = 10 80.0	n = 14 50.0	n = 24 62.5	n = 10 60.0	n = 14 35.7	n = 24 45.8	n = 10 0.25	n = 14 0.37	n = 24 0.32
Week 84	n = 10 0.00	n = 10 1.95	n = 20 0.70	n = 10 80.0	n = 10 60.0	n = 20 70.0	n = 10 70.0	n = 10 50.0	n = 20 60.0	n = 10 0.30	n = 10 0.41	n = 20 0.36

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; Q3W = every 3 weeks; Q4W = every 4 weeks; 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 pJIA, a physician global VAS ≤ 10 mm, and a normal ESR [< 20 mm/hr]).

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

Source: WA29231:t_ef_SE_JADAS_C, t_ef_prop_SE_INACT, t_ef_prop_SE_REMIS and t_ef_SE_CHAQ_C.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study WA28117 is a Phase Ib, open-Label, multicentre study to investigate the pharmacokinetics, pharmacodynamics, and safety of tocilizumab following SC administration to patients with polyarticular juvenile idiopathic arthritis.

The sample size considerations cannot be fully assessed as the simulations cannot be replicated. However, sample size considerations as presented are deemed appropriate.

There were 2 global and one country specific study protocol amendments. These amendments do not impact the safety and efficacy analysis of the study. Four patients had protocol violations; these protocol violations are not expected to impact the analysis of the study data.

Study WA19977 was the pivotal study to support the efficacy and safety in "active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

In the TCZ IV Study WA19977, the JIA ACR response was used as the primary efficacy endpoint measure. However in 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).

In general the development program is in line with the CHMP Scientific Advice.

Efficacy data and additional analyses

Overall, the interpretation of the results is hampered by the small sample sizes. However, these exploratory data are considered supportive in addition to the robust pharmacological data. Further the efficacy of TCZ in the treatment pJIA was confirmed with the TCZ IV (see AR variation II/26). Thus the small sample size in this context is not a concern.

The 52 patients enrolled into study WA28117 were predominantly female and Caucasian. As expected the median age and height were all higher in the > 30 kg BW group compared with the < 30 kg BW group, which was as expected for these BW dosing groups. Demographic and baseline disease characteristics at baseline were generally well balanced between the two BW groups.

In both BW groups, JADAS-71 generally improved (decreased) over the course of Study WA28117 for TCZ naive patients, and was maintained for prior TCZ patients (who had switched from TCZ IV to TCZ SC at study entry).

In the TCZ naive patients weighing < 30 kg (n=23), the median JADAS-71 reduced to the level of inactive disease (< 1.0) by Week 27, and generally remained at this level for the rest of the study. In the TCZ naive patients weighing > 30 kg (n=14), the median JADAS-71 dropped to near minimal disease activity (< 3.8) by Week 20, and remained essentially at this level throughout the rest of the study. Decreases in the JADAS-71 components were reported to be more pronounced for the < 30 kg BW group compared to the > 30 kg BW group, with the exception of ESR, where reductions were comparable for both BW groups. Prior TCZ patients had lower baseline scores compared with the TCZ naive patients in both BW groups. These patients who entered the study while receiving TCZ IV treatment were able to maintain disease control, as reflected by JADAS-71, upon their transition to TCZ SC.

Pain was assessed using a 0 - 100 mm VAS, with 0 for no pain and 100 mm for very extreme pain. Among the TCZ naive patients, the pain VAS continued to decrease over the first 27 weeks for the < 30 kg group, and the first 36 weeks for the > 30 kg group, and essentially remained at this level for both BW groups for the rest of the study. The prior TCZ patients in both BW groups had low pain VAS at baseline, with further reduction of pain observed up to Week 18 in the < 30 kg group, and up to Week 36 in the > 30 kg group, remaining low through the end of the study. Prior TCZ patients had lower baseline scores compared with the TCZ naive patients in both BW groups, and the low scores were, importantly, maintained throughout the study.

Inactive disease was defined as no joints with active arthritis, no fever or physical exam features (including active uveitis) attributable to pJIA, a physician global VAS $\leq$ 10 mm, and a normal ESR (< 20 mm/hr). By BW, irrespective of TCZ status, 80.0% (20/25) of patients weighing < 30 kg had inactive disease at Week 51, and 59.1% (13/22) of patients weighing $\geq$ 30 kg had inactive disease at Week 52.

Clinical remission was defined as inactive disease for a minimum of 6 continuous months irrespective of disease-modifying anti-rheumatic drug, non-steroidal anti-inflammatory drug, or corticosteroid use. By BW group, irrespective of TCZ status, 11/25 (44.0%) of patients weighing < 30 kg and 5/22 (22.7%) of patients weighing $\geq$ 30 kg achieved clinical remission at the end of the study.

The CHAQ-DI was completed to evaluate functional ability at a scale of 0 (best) to 3 (worst). Progressive improvement in mean CHAQ-DI scores ($\pm$ SD) was generally observed in the All TCZ naive patients through the end of the study. A greater improvement in the mean CHAQ-DI scores at the end of the study was observed in the < 30 kg BW group compared with the $\geq$ 30 kg BW group for both TCZ naive and prior TCZ patients.

Results from exploratory endpoints showed that TCZ SC improved (in TCZ naïve patients) or maintained (in prior TCZ patients) efficacy for all parameters evaluated over the course of the study for patients in both BW groups (< 30 kg and $\geq$ 30 kg). The improvement of efficacy endpoints was more pronounced in the lower BW group and this shed some doubts if the proposed dosage and regimen was adequate. A post-hoc efficacy analysis in terms of dose/kg as proposed in the CHMP SA was submitted. The analysis showed, although the sample size was small, that there was no clear trend observed between efficacy and the normalised dose as measured by mg/kg/week for both the SC Q3W and Q2W dosing regimens, for both patients initiating TCZ and for patients who switched from TCZ IV to TCZ SC at baseline.

Comparative efficacy analysis of the TCZ SC efficacy data (Study WA 28117) with TCZ IV (Study WA19977) is 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.

Patient demographics at baseline, disease characteristics and previous or concomitant medication use in the TCZ naive SC patients (WA28117) were generally comparable with those in the TCZ IV Study WA19977 with two exceptions: Higher proportion of TCZ naive SC patients in the higher weight group received prior biologic DMARDs (71%) compared with patients in the same weight group in the TCZ IV study (39%), and the TCZ naive SC patients had lower disease activity and better physical function at baseline, as measured by median JADAS-71 and mean CHAQ-DI scores compared with the TCZ IV study patients. The lower median JADAS-71 and mean CHAQ-DI scores in the TCZ SC population might be attributed to the higher use of prior biologic DMARDs in these patients.

Overall, similar median JADAS-71 results were observed with TCZ SC and TCZ IV when comparing the All TCZ naive patients from WA28117 with the All TCZ patients from WA19977 at Week 12 (6.60 vs. 6.50), Week 36 (1.75 vs. 2.60), and Week 51/52 (1.20 vs.1.60). By BW, similar efficacy trends in the median or mean JADAS-71 were also observed when comparing between TCZ naive SC and TCZ IV.

The proportion of patients with inactive disease at Week 51/52 was numerically higher for the TCZ naive SC patients from WA28117 (64.5%) versus TCZ IV patients from WA19977 (52.4%).

The proportion of patients who achieved clinical remission at Week 51/52 was numerically higher for TCZ naive SC patients from WA28117 (27.0%) versus TCZ IV patients from WA19977 (18.3%). A numerically higher proportion of patients in the < 30 kg BW group achieved clinical remission with TCZ SC (34.7%) versus TCZ IV (22.2%), whereas the proportion of patients weighing $\geq$ 30 kg achieving clinical remission was comparable for TCZ SC (14.2%) versus TCZ IV (18.2%).

Progressive improvement in mean CHAQ-DI scores was generally observed in TCZ naive SC patients with similar improvement also observed in TCZ IV patients. By BW, the improvement in the mean CHAQ-DI scores between the TCZ naive SC and TCZ IV patients weighing < 30 kg at Week 51/52 were consistent (- 65.7% vs. - 67.1% mean CFB, respectively). In the $\geq$ 30 kg BW group, the improvement in mean CHAQ-DI scores for the TCZ naive SC patients at Week 52 (- 27.9% mean CFB) was less than that observed for the patients in the same weight group in the TCZ IV Study WA19997 at Week 52 (- 74.9% mean CFB).

Overall normal growth patterns were observed after 1 year of TCZ treatment for both the TCZ SC WA28117 and TCZ IV WA19977 studies.

Further supportive LTE efficacy data are provided from 41 patients with pJIA who were enrolled in Study WA29231 at the time of the clinical cut-off date (17 July 2016). The efficacy results from LTE Study WA29231 showed that TCZ SC improved or maintained efficacy for all parameters evaluated up to Week 84 for both BW groups (< 30 kg and $\geq$ 30 kg), with the limitation that data were based on a limited sample size.

2.4.4. Conclusions on the clinical efficacy

Exploratory efficacy evaluation and comparative analysis of the TCZ SC efficacy data (Study WA 28117) with TCZ IV (Study WA19977) is provided. Comparing TCZ naïve patients through Week 52 from Study WA28117 with TCZ IV efficacy data from the "continuous TCZ" IV subgroup through Week 52 from Study WA19977 revealed comparable efficacy (JADAS-71, clinical remission, inactive disease and CHAQ-DI score).

Overall normal growth patterns were observed after 1 year of TCZ treatment for both the TCZ studies.

2.5. Clinical safety

Introduction

The main study contributing to the safety evaluation of TCZ SC in pJIA is the 52-week randomized open-label Phase 1b pharmacokinetic (PK)/ pharmacodynamic (PD) bridging Study WA28117. The safety analyses are based on final data from 52 pJIA patients who received TCZ SC for a total duration of 50.43 patient years (PY).

The final TCZ SC safety data from Study WA28117 are compared with intravenous (IV) TCZ safety data from Study WA19977, the pivotal Phase III study for the approval of the IV formulation of TCZ in pJIA patients in 2013.

Supportive data on the long-term safety of TCZ SC in patients with pJIA are provided from 41 pJIA patients in Study WA29231, the ongoing open-lab long-term extension (LTE) of Study WA28117. The analyses are based on data collected up to a clinical cut-off date of 17 July 2016, which contribute an

additional duration of 47.51 PYs.

For the analyses of injection site reactions (ISRs), which are specific to the SC mode of administration, the ISR data from TCZ SC Study WA28117 are compared with corresponding ISR data from the two pivotal Phase III trials with TCZ SC in adult patients with rheumatoid arthritis (RA); Study WA22762 and Study NA25220. All ISR analyses are based on data from patients who received TCZ SC via a pre-filled syringe (PFS) with needle safety device (NSD).

Patient exposure

The WA28117 All TCZ SC population provides safety data from 52 pJIA patients who received at least one dose of open-label TCZ SC.

The WA19977 Week 40 All TCZ IV safety population provides safety data from 188 pJIA patients who received at least one dose of TCZ IV.

As of the clinical cut-off date (17 July 2016), a total of 41 pJIA patients from Study WA28117 received at least one dose of TCZ SC in LTE Study WA29231 and are included in the WA29231 All TCZ SC LTE safety population.

Table 16 - Summary of exposure to study drug in Studies WA2811 (TCZ SC), WA29231 (TCZ SC LTE), and WA1977 (TCZ IV) in pJIA

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[b]
Duration in study (years)[c]									
Mean (SD)	0.99 (0.09)	0.95 (0.14)	0.97 (0.12)	1.05 (0.66)	1.27 (0.54)	1.16 (0.61)	0.88 (0.42)	1.04 (0.45)	0.98 (0.45)
Median	0.98	1.00	0.99	0.69	1.50	1.40	0.85	1.02	0.93
Min-Max	0.7-1.1	0.5-1.1	0.5-1.1	0.0-1.8	0.1-1.9	0.0-1.9	0.3-1.7	0.1-1.9	0.1-1.9
Sum	26.60	23.83	50.43	22.08	25.43	47.51	24.68	123.94	184.44
Treatment duration (years)[d,e,f]									
Mean (SD)	0.95 (0.09)	0.95 (0.15)	0.95 (0.12)	1.08 (0.66)	1.26 (0.55)	1.17 (0.61)	0.83 (0.47)	1.01 (0.48)	0.94 (0.49)
Median	0.98	1.00	0.98	0.71	1.50	1.42	0.83	0.99	0.92
Min-Max	0.6 - 1.0	0.5 - 1.0	0.5 - 1.0	0.1 – 1.9	0.0 – 1.9	0.0 – 1.9	0.2 - 1.7	0.0 - 1.8	0.0 - 1.8

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

a Data on placebo treatment received in Part II (withdrawal phase) of Study WA19977 are excluded.

b The 'All TCZ IV' group includes all patients in the WA19977 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 group and is used to calculate AE rates per 100 PY.

d Treatment duration (days) = (date of last injection - date of first injection +15)/365.25 for patients on TCZ SC Q2W.

e Treatment duration (days) = (date of last injection - date of first injection +22)/365.25 for patients on TCZ SC Q3W.

f Treatment duration (days) =(date of last infusion - date of first infusion + 1) - exposure to placebo treatment/365.25 for patients on TCZ IV Q4W. Referred to as 'Exposure to TCZ' in WA19977 source output.

Source WA28117: Table 9 in WA28117 CSR; Source W29231: t_ex_SE ; Source WA19977: Table 36 in 40-Week WA19977 CSR.

The total study duration, which is used to calculated rates of AEs per 100 patient years (PY), was 50.43 PY in TCZ SC Study WA28117, 47.51 PY in TCZ SC LTE Study WA29231, and 184.44 PY in TCZ IV Study WA19977.

Adverse events

Table 17 - Adverse event rates in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[b]
Duration in study (PY)	26.60	23.83	50.43	22.08	25.43	47.51	24.68	123.94	184.44
AE									
Total no. AEs	181	225	406	125	153	278	110	622	885
Rate per 100 PY (95% CI)	680.5 (584.93,787.13)	944.2 (824.84,1075.96)	805.1 (728.66,887.33)	566.1 (471.24,674.51)	601.7 (510.10,704.90)	585.1 (518.37,658.12)	445.6 (366.32,537.20)	501.9 (463.19,542.89)	479.8 (448.73,512.51)
SAE									
Total no. AEs	2	2	4	1	3	4	3	18	23
Rate per 100 PY (95% CI)	7.5 (0.91,27.16)	8.4 (1.02,30.32)	7.9 (2.16,20.31)	4.5 (0.11, 25.23)	11.8 (2.43, 34.48)	8.4 (2.29, 21.56)	12.2 (2.51,35.52)	14.5 (8.61,22.95)	12.5 (7.91,18.71)
AE leading to withdrawal									
Total no. AEs	0	0	0	0	1	1	1	3	6
Rate per 100 PY (95% CI)	-	-	-	-	3.9 (0.10 21.91)	2.1 (0.05, 11.73)	4.1 (0.10,22.58)	2.4 (0.50, 7.07)	3.3 (1.19, 7.08)
AE leading to dose interruption									
Total no. AEs	10	3	13	10	3	13	NA	NA	NA
Rate per 100 PY (95% CI)	37.6 (18.03, 69.14)	12.6 (2.60, 36.79)	25.8 (13.73, 44.08)	45.3 (21.72,83.29)	11.8 (2.43,34.48)	27.4 (14.57,46.79)	NA	NA	NA

Table 18 - Overview of key adverse events in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N =21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[b]
Total no. of patients with at least one:									
AE	25 (92.6%)	23 (92.0%)	48 (92.3%)	17 (81.0%)	17 (85.0%)	34 (82.9%)	26 (92.9%)	102 (85.7%)	159 (84.6%)
SAE	1 (3.7%)	2 (8.0%)	3 (5.8%)	1 (4.8%)	2 (10.0%)	3 (7.3%)	3 (10.7%)	12 (10.1%)	17 (9.0%)
AE with fatal outcome	0	0	0	0	0	0	0	0	0
AE leading to withdrawal from treatment	0	0	0	0	1 (5.0%)	1 (2.4%)	1 (3.6%)	3 (2.5%)	6 (3.2%)
AE leading to dose interruption	4 (14.8%)	2 (8.0%)	6 (11.5%)	5 (23.8%)	2 (10.0%)	7 (17.1%)	8 (28.6%)	13 (10.9%)	24 (12.8%)
AESI/Selected AE:									
Infection	20 (74.0%)	16 (64.0%)	36 (69.2%)	16 (76.2%)	10 (50.0%)	26 (63.4%)	19 (67.9%)	76 (63.9%)	115 (61.2%)
Serious infection	1 (3.7%)	0	1 (1.9%)	1 (4.8%)	1 (5.0%)	2 (4.9%)	3 (10.7%)	5 (4.2%)	9 (4.8%)
Anaphylactic reaction (SMQ Narrow)	0	0	0	0	0	0	0	0	0
Anaphylactic reaction (Sampson's Criteria)	1 (3.7%)	0	1 (1.9%)	0	0	0	0	0	0
Injection site reaction	4 (14.8%)	11 (44.0%)	15 (28.8%)	1 (4.8%)	6 (30.0%)	7 (17.1%)	NA	NA	NA
Neutropenia	4 (14.8%)	1 (4.0%)	5 (9.6%)	3 (14.3%)	1 (5.0%)	4 (9.8%)	0	0	0
Thrombocytopenia	0	0	0	0	0	0	1 (3.6%)	1 (0.8%)	2 (1.1%)

- **Study WA28117**

The majority of pJIA patients (48/52 [92.3%]) in Study WA28117 had at least one AE during treatment; 25/27 (92.6%) patients in the < 30 kg BW group and 23/25 (92.0%) patients in the > 30 kg BW group.

For most of the patients with an AE (42/48 patients), the highest NCI grade experienced was Grade 1 or Grade 2 (WA28117 CSR). Four patients (7.7%; 3 patients < 30 kg BW and 1 patient > 30 kg BW) experienced a Grade 3 AE (neutrophil count decreased, neutropenia, varicella, and arthralgia), and 2 patients (3.8%, both < 30 kg BW) experienced a Grade 4 AE (neutropenia and croup infectious).

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

- Infections and Infestations (36/52 [69.2%]) – most commonly nasopharyngitis (18/52 [34.6%]);

- Musculoskeletal and Connective Tissue Disorders (23/52 [44.2%]) – most commonly arthralgia (9/52 [17.3%]);

- Gastrointestinal Disorders (21/52 [40.4%]) – most commonly vomiting (9/52 [17.3%]);

- General Disorders and Administration Site Conditions (20/52 [38.5%]) – most commonly injection site erythema (10/52 [19.2%]);

- Respiratory, Thoracic and Mediastinal Disorders (18/52 [34.6%]) – most commonly cough (13/52 [25.0%])

- Skin and Subcutaneous Tissue Disorders (12/52 [23.1%]) – most commonly eczema (5/52 [9.6%])

- Nervous System Disorders (10/52 [19.2%]) – most commonly headache (7/52 [13.5%])

- Psychiatric Disorders (8/52 [15.4%]) – most commonly insomnia (4/52 [7.7%])

By preferred term, the most commonly reported AEs, irrespective of treatment relationship, were nasopharyngitis (18/52 patients [34.6%]) and cough (13/52 patients [25.0%]). Other AEs reported in > 10% of patients were injection site erythema (19.2%), arthralgia (17.3%), vomiting (17.3%), headache (13.5%), abdominal pain (11.5%), gastroenteritis (11.5%), nausea (11.5%), pyrexia (11.5%), diarrhoea (9.6%), eczema (9.6%), pain in extremity (9.6%), and upper respiratory tract infection (9.6%)

The overall rate of AEs in the WA28117 All TCZ SC population was 805.1 [95% CI: 728.66, 887.33] AEs per 100 PY based on a total of 406 AEs. This is higher than the rate observed in the WA19977 All TCZ IV Week 40 population (479.8 [95% CI: 448.73, 512.51] AEs per 100 PY)

Table 19 - Primary preferred terms (excluding ISRs) contributing to the higher overall AE rate in TCZ SC Study WA28117 compared with TCZ IV Study WA19977 (Safety Population)

Preferred Term	Study WA28117 (Week 52) All TCZ SC N = 52	Study WA19977 (Week 40)[a] All TCZ IV N = 188
Duration in study (PY)	50.43	184.44
Nasopharyngitits		
No. pts (%)	18 (34.6%)	39 (20.7%)
Total no. AEs	26	56
Rate per 100 PY (95% CI)	51.6 (33.68, 75.54)	30.4 (22.94, 39.43)
Cough		
No. pts (%)	13 (25.0%)	18 (9.6%)
Total no. AEs	20	22
Rate per 100 PY (95% CI)	39.7 (24.22, 61.25)	11.9 (7.48, 18.06)
Arthralgia		
No. pts (%)	9 (17.3%)	6 (3.2%)
Total no. AEs	17	10
Rate per 100 PY (95% CI)	33.7 (19.64, 53.97)	5.4 (2.60, 9.97)
Vomiting		
No. pts (%)	9 (17.3%)	14 (7.4%)
Total no. AEs	15	17
Rate per 100 PY (95% CI)	29.7 (16.65, 49.06)	9.2 (5.37, 14.76)
Neutropenia		
No. pts (%)	4 (7.7%)	0
Total no. AEs	10	0
Rate per 100 PY (95% CI)	19.8 (9.51, 36.47)	-
Gastroenteritis		
No. pts (%)	6 (11.5%)	7 (3.7%)
Total no. AEs	9	9
Rate per 100 PY (95% CI)	17.8 (8.16, 33.88)	4.9 (2.23, 9.26)
Pain in extremity		
No. pts (%)	5 (9.6%)	3 (1.6%)
Total no. AEs	8	3
Rate per 100 PY (95% CI)	15.9 (6.85, 31.26)	1.6 (0.34, 4.75)

[a] Data on placebo treatment received in Part II (withdrawal phase) of Study WA19977 are excluded.

Excludes ISR-related AEs.

Source WA28117: t_ae_grade_SE and t_ae_rate_SE_NOSPLT in WA28117 CSR.

Source WA19977: stae11_ae and staerate02_otrt_npbo_se_p123a in 40-Week WA19977 CSR.

Body weight subgroups

Analysis of the WA28117 data by body weight group showed a higher AE rate in patients in the ≥ 30 kg BW group compared with patients in the < 30 kg BW group (944.2 [95%CI: 824.84, 1075.96] vs. 680.5 [584.93, 787.13], respectively).

The higher overall AE rate in patients weighing ≥ 30 kg was primarily driven by higher AE rates in the Musculoskeletal and Connective Tissue Disorders (mostly arthralgia, pain in extremity, and joint swelling), Gastrointestinal Disorders (mostly nausea), General Disorders and Administration Site Conditions (mostly ISR-related AEs and Nervous System Disorders (mostly headache) SOCs. Conversely, higher AE rates were observed in patients in the < 30 kg BW group compared with patients in the ≥ 30 kg BW group in the Infections and Infestations (mostly nasopharyngitis and gastroenteritis and Blood and Lymphatic System Disorders.

- **LTE Study WA29231**

At the time of the clinical cut-off for the SCS (17 July 2016), 34/41 (82.9%) pJIA patients in LTE Study WA29231 had experienced a total of 278 AEs; 17/21 (81.0%) patients in the < 30 kg BW group and 17/20 (85.0%) patients in the ≥ 30 kg BW group.

Table 20 - Most commonly reported adverse events (≥ 10% of patients by preferred term (LTE Study WA29231, safety population

MedDRA Preferred Term	TCZ SC 162 mg Q3W (< 30 kg) (N=21)	TCZ SC 162 mg Q2W (>= 30 kg) (N=20)	All TCZ (N=41)
Total number of patients with at least one adverse event	17 (81.0%)	17 (85.0%)	34 (82.9%)
Total number of events	125	153	278
NASOPHARYNGITIS	6 (28.6%)	5 (25.0%)	11 (26.8%)
ARTHRALGIA	4 (19.0%)	3 (15.0%)	7 (17.1%)
VOMITING	4 (19.0%)	3 (15.0%)	7 (17.1%)
DIARRHOEA	4 (19.0%)	2 (10.0%)	6 (14.6%)
GASTROENTERITIS	5 (23.8%)	1 (5.0%)	6 (14.6%)
HEADACHE	1 (4.8%)	4 (20.0%)	5 (12.2%)
OROPHARYNGEAL PAIN	1 (4.8%)	4 (20.0%)	5 (12.2%)
COUGH	4 (19.0%)	0	4 (9.8%)
INJECTION SITE ERYTHEMA	1 (4.8%)	3 (15.0%)	4 (9.8%)
NEUTROPENIA	3 (14.3%)	1 (5.0%)	4 (9.8%)
PYREXIA	3 (14.3%)	1 (5.0%)	4 (9.8%)

Investigator text for AEs encoded using MedDRA version 19.0.
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.

Adapted from Program: /opt/BIOSTAT/prod/cn11935h/i29231b/t_ae.sas
Output: /opt/BIOSTAT/prod/cn11935h/i29231b/reports/t_ae_SE_PREF.out
19OCT2016 18:03

Body weight subgroups

The overall AE rate was similar in the two BW subgroups; 566.1 [95% CI: 471.24, 674.51] in the ≤ 30 kg BW group and 601.7 [95% CI: 510.10, 704.90] in the ≥ 30 kg BW group (see Table S2).

Consistent with results in Study WA28117, SOCs with a notably higher AE rate in patients in the ≥ 30 kg BW group were Musculoskeletal and Connective Tissue Disorders (mostly arthralgia) and General Disorders and Administration Site Conditions (mostly ISR-related AEs), whereas SOCs with a notably higher AE rate in the < 30 kg BW group were Infections and Infestations (mostly due to differences in rates of gastroenteritis and ear infection) and Blood and Lymphatic System Disorders (mostly neutropenia).

The LTE WA29231 Musculoskeletal and Connective Tissue Disorders SOC AE rate was 67.9 [95% CI: 38.02, 112.05] AEs per 100 PY in the <30 kg BW group and 106.2 [95% CI: 69.97, 154.48] AEs per 100 PY in the < 30 kg group. Closer analysis of the data in the ≥ 30 kg BW group shows that 1 patient, experienced 12 of the 27 (44.4%) Musculoskeletal and Connective Tissue Disorders SOC AEs, which includes 10 of the 12 (83.3%) arthralgia AEs reported up to the clinical cut-off within the ≥ 30 kg BW group. This patient also reported 12 AEs within the Musculoskeletal and Connective Tissue Disorders SOC during WA28117.

Immunogenicity

There was a higher incidence of immunogenicity in the pJIA TCZ SC program (5 of 52 patients, 9.6%) compared with the TCZ IV Study WA19977 (1 of 188 patients, 0.5%). However a robust comparison is hampered by the small sample size.

Serious adverse event/deaths/other significant events

No deaths were reported in TCZ SC Studies WA28117 and WA29231 or in TCZ IV Study WA19977.

- **Study WA28117**

A total of 4 SAEs were reported by 3/52 (5.8%) patients during Study WA28117; one patient in the < 30 kg BW group reported 2 SAEs and two patients in the ≥ 30 kg BW group reported one SAE each:

- A SAE of infectious croup (Grade 4) and a Grade 3 varicella.

- A Grade 2 decreased appetite.

- A Grade 3 arthralgia SAE.

- The rate of SAEs based on the 4 events was 7.9 (95% CI: 2.61, 20.31) SAEs per 100 PY.

- **LTE Study WA29231**

In LTE Study WA29231, 3/41 (7.3%) patients experienced a total of 4 SAEs up to the clinical cut-off date

- One patient was hospitalised with Grade 3 pneumonia SAE.

- One patient experienced a Grade 3 SAE of eye pain followed by a Grade 3 SAE of headache.

- One patient experienced a SAE of Grade 3 infectious mononucleosis

- The WA29231 SAE rate based on the 4 events was 8.4 [95% CI: 2.29, 21.56] SAEs per 100 PY.

Adverse events of special interest

Table 21 - Incidence of AESIs and selected AES in pJIA treated SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			LTE Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27 No pts (%)	TCZ SC Q2W (≥ 30 kg) N = 25 No pts (%)	All TCZ SC N = 52 No pts (%)	TCZ SC Q3W (< 30 kg) N = 21 No. (%)	TCZ SC Q2W (≥ 30 kg) N = 20 No. (%)	All TCZ SC LTE N = 41 No. (%)	10 mg/kg Q4W (< 30 kg) N = 28 No. (%)	8 mg/kg Q4W (≥ 30 kg) N = 119 No. (%)	All TCZ IV N = 188[b] No. (%)
AESIs									
Serious infections	1 (3.7%)	0 (0.0%)	1 (1.9%)	1 (4.8%)	1 (5.0%)	2 (4.9%)	3 (10.7%)	12 (10.1%)	17 (9.0%)
Opportunistic infections	0	0	0	0	0	0	0	0	0
Hypersensitivity reactions [c]	3 (11.1%)	1 (4.0%)	4 (7.7%)	1 (4.8%)	0	1 (2.4%)	2 (7.1%)	24 (20.2%)	33 (17.6%)
Anaphylactic reactions									
Sampson's Criteria	1 (3.7%)	0	1 (1.9%)	0	0	0	0	0	0
SMQ Narrow	0	0	0	0	0	0	0	0	0
Injection site reactions	4 (14.8%)	11 (44.0%)	15 (28.8%)	1 (4.8%)	6 (30.0%)	7 (17.1%)	NA	NA	NA
Hepatic SAEs	0	0	0	0	0	0	0	1 (0.8%)	1 (0.5%)
Other AESIs [d]	0	0	0	0	0	0	0	0	0
Additional selected AEs									
Infection AE	20 (74.1%)	16 (64.0%)	36 (69.2%)	16 (76.2%)	10 (50.0%)	26 (63.4%)	19 (67.9%)	76 (63.9%)	115 (61.2%)
Neutropenia AEs	4 (14.8%)	1 (4.0%)	5 (9.6%)	3 (14.3%)	1 (5.0%)	4 (9.8%)	0	0	0
Thrombocytopenia AEs	0	0	0	0	0	0	1 (3.6%)	1 (0.8%)	2 (1.1%)

AESI = adverse event of special interest; IV = intravenous; LTE = long-term extension; NA = not applicable; Q2/3/4W = every 2/3/4 weeks;
  SC = subcutaneous; SD = standard deviation; SMQ = standard MedDRA query ; TCZ = tocilizumab.

[a] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA19977 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 gastrointestinal perforations, demyelinating disorders, myocardial infarction / acute coronary syndrome, stroke, serious bleeding, and malignancies.

Source WA28117 CSR: Table 8 and Section 6.8 in W28117 CSR.

Source WA29231: t_ae_SE; t_ae_SE_SAE; t_ae_rate_SE_ATINJ24_NUNREL ; t_ae_rate_SE_ANA ; t_ae_rate_SE_SAMP ; t_ae_rate_SE_ISR ;
t_ae_rate_SE_SAE_HEP ; I_ae_SE_GIPERF ; t_ae_rate_SE_MALIG ; t_ae_rate_SE_DMY; t_ae_rate_SE_SAE_MYINF;
t_ae_rate_SE_SAE_STRK ; t_ae_rate_SE_NEUT ; t_ae_rate_SE_THROM.

Source WA19977: Section 7.9 in 40-Week WA19977 CSR.

Infections

Table 22 - Rate of infections in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[b]
Duration in study (PY)	26.60	23.83	50.43	22.08	25.43	47.51	24.68	123.94	184.44
Infection AE									
No. pts (%)	20 (74.1%)	16 (64.0%)	36 (69.2%)	16 (76.2%)	10 (50.0%)	26 (63.4%)	19 (67.9%)	76 (63.9%)	115 (61.2%)
Total no. AEs	56	29	85	40	25	65	49	199	302
Rate per 100 PY (95% CI)	210.5 (159.03,273.39)	121.7 (81.50,174.77)	168.6 (134.63,208.42)	181.2 (129.42,246.69)	98.3 (63.62,145.12)	136.8 (105.59,174.38)	198.5 (146.88,262.48)	160.6 (139.03,184.49)	163.7 (145.79,183.29)
Serious infections									
No. pts (%)	1 (3.7%)	0 (0.0%)	1 (1.9%)	1 (4.8%)	1 (5.0%)	2 (4.9%)	3 (10.7%)	5 (4.2%)	9 (4.8%)
Total no. AEs	2	0	2	1	1	2	3	5	9
Rate per 100 PY (95% CI)	7.5 (0.91,27.16)	-	4.0 (0.48,14.33)	4.5 (0.11,25.23)	3.9 (0.10,21.91)	4.2 (0.51,15.21)	12.2 (2.51, 35.52)	4.0 (1.31, 9.41)	4.9 (2.23, 9.26)
Opportunistic infections									
No. pts (%)	0	0	0	0	0	0	0	0	0

LTE = long-term extension; IV = intravenous; PY = patient years Q2/3/4W = every 2/3/4 weeks; SC = subcutaneous; TCZ = tocilizumab.
[a] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.
[b] The 'All TCZ IV' group includes all patients in the WA19977 safety population including those in dose groups not shown.
Source WA28117: Sections 6.8.1 and 6.8.2 in WA28117 CSR.
Source WA29231: t_ae_SE, t_ae_rate_SE, t_ae_SE_SAE_INF, t_ae_rate_SE_SAE_INF.
Source WA19977: Section 7.9.1 in 40-Week WA19977 CSR.

The rate of infection AEs in the WA28117 All TCZ SC safety population (168.6 [95% CI 134.63, 208.42] AEs per 100 PY) was comparable with that in the WA19977 All TCZ IV Week 40 safety population (163.7 [95% CI: 145.79,183.29] AEs per 100 PY) indicating no increase in rate of infection with the SC regimen compared with the IV regimen.

The most frequent infection AEs (occurring in ≥ 10% of patients) in the WA28117 All TCZ SC safety population were nasopharyngitis (34.6%), gastroenteritis (11.5%), and upper respiratory tract infection (9.6%).

The rate of infection AEs in the WA29231 All TCZ SC LTE safety population (136.8 [95% CI: 105.59,174.38]) was numerically lower than the rate in the WA28117 All TCZ SC safety population indicating no increase in the rate of infection AEs over time in pJIA patients receiving TCZ SC.

In TCZ SC Study WA28117, infection AEs was more common in TCZ naïve patients than in patients who had previously received TCZ.

In TCZ SC Studies WA28117 and WA29231, infection AEs was more common in the < 30 kg BW group than in the ≥ 30 kg BW group.

Of the 85 infection AEs reported during TCZ SC Study WA28117, two infections in one patient in the < 30 kg BW group were reported as SAEs; croup infectious (Grade 4) and varicella (Grade 3). Both SAEs resolved.

Two (4.9%) patients experienced an infection SAE in LTE study WA29231 up to the clinical cut-off date. One patient in the < 30 kg BW subgroup experienced pneumonia (Grade 3) and one patient in the ≥ 30 kg subgroup experienced infectious mononucleosis (Grade 3). Both events resolved.

No opportunistic infections were reported in TCZ SC Studies WA28117 or WA29231.

Analysis of the WA28117 TCZ SC data by previous TCZ use (TCZ naive vs. prior TCZ) showed that infection AEs were more common among TCZ naive patients compared with prior TCZ patients, both in terms of incidence (27/37 [73.0%] vs. 9/15 [60.0%], respectively) and rate (200.9 [95% CI: 157.19, 252.99] vs. 89.2 [95% CI: 47.48, 152.47] AEs per 100 PY, respectively). The higher incidence of infection AEs in TCZ naive patients was primarily driven by higher frequencies ($\Box$ 10% difference) of nasopharyngitis (14/37 [37.8%] vs. 4/15 [26.7%]) and upper respiratory tract infection (5/37 [13.5%] vs. 0/15 [0.0%])

Hypersensitivity and anaphylactic reactions

Table 23 - Rate of hypersensitivity and anaphylactic relations in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[b]
Duration in study (PY)	26.60	23.83	50.43	22.08	25.43	47.51	24.68	123.94	184.44
Hypersensitivity reactions									
No. pts (%)	3 (11.1%)	1 (4.0%)	4 (7.7%)	1 (4.8%)	0	1 (2.4%)	2 (7.1%)	24 (20.2%)	33 (17.6%)
Total no. AEs	3	2	5	1	-	1	3	31	43
Rate per 100 PY (95% CI)	11.3 (2.33, 32.96)	8.4 (1.02, 30.32)	9.9 (3.22, 23.14)	4.5 (0.11,25.23)	-	2.1 (0.05,11.73)	12.2 (2.51,35.52)	25.0 (16.99,35.50)	23.3 (16.87, 31.40)
Anaphylactic reactions (SMQ Narrow)									
No. pts (%)	0	0	0	0	0	0	0	0	0
Anaphylactic reactions (Sampson's Criteria)									
No. pts (%)	1 (3.7%)	0	1 (1.9%)	0	0	0	0	0	0
Total no. AEs	1[c]	0	1[c]	-	-	-	-	-	-
Rate per 100 PY (95% CI)	7.5 (0.91, 27.16)	-	4.0 (0.48, 14.33)	-	-	-	-	-	-

LTE = long-term extension; IV = intravenous; PY = patient years Q2/3/4W = every 2/3/4 weeks; SC = subcutaneous; TCZ = tocilizumab.
Hypersensitivity reactions were all AEs that occurred during or within 24 hours of an injection (excluding ISRs) or infusion that were not deemed 'unrelated' to study medication.
[a] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.
[b] The 'All TCZ IV' group includes all patients in the WA19977 safety population including those in dose groups not shown.
[c] An independent adjudication confirmed that this AE did not represent a systemic anaphylactic reaction.
Source WA28117: Table 15 and Section 6.8.3.2 in WA28117 CSR.
Source WA29231: t_ae_rate_SE_ATINJ24_NUNREL.
Source WA19977: Section 7.9.2.2 and 7.9.2.3 in 40-Week WA19977 CSR.

The rate of potential hypersensitivity reaction AEs in the WA28117 All TCZ SC population (9.9 [95% CI: 3.22, 23.14] AEs per 100 PY) was numerically lower than the rate of potential hypersensitivity AEs observed during or within 24 hours of an infusion in the WA19977 All TCZ IV Week 40 safety population (23.3 [95% CI: 16.87, 31.40] AEs per 100 PY).

All potential hypersensitivity reaction AEs in TCZ SC Studies WA28117 and WA29231 were non-serious Grade 1 events.

No anaphylactic reactions occurred in TCZ SC Studies WA28117 and WA29231. One patient was identified as having non-serious Grade 1 signs and symptoms of a potential anaphylactic reaction according to Sampson's criteria; however an independent adjudication confirmed that it did not represent a systemic anaphylactic reaction.

Injection site reactions

ISR rates are calculated by two methods. In the standard calculation of ISR rates per 100 PY, all individual ISR AEs (i.e., all the clinical signs and symptoms of an ISR reported as individual AEs) are

counted individually. In the calculation of ISR episodes, which is required for comparison with data from the adult RA studies, individual ISR AEs occurring at a single injection site in the same injection interval are counted together as one episode.

Table 24 - rate of injection site reactions in pJIA patients treated with TCZ SC (Studies WA28117 and WA29231) (safety populations)

	Study WA28117 (Week 52)			LTE Study WA29231 (Cut-off July 2016)		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41
Duration in study (PY)	26.60	23.83	50.43	22.08	25.43	47.51
No. pts (%)	4 (14.8%)	11 (44.0%)	15 (28.8%)	1 (4.8%)	6 (30.0%)	7 (17.1%)
ISRs[a]						
Total no. AEs	10	47	57	4	48	52
Rate per 100 PY (95% CI)	37.6 (18.03,69.14)	197.2 (144.92, 262.27)	113.0 (85.61,146.44)	18.1 (4.94,46.38)	188.8 (139.17, 250.26)	109.5 (81.74,143.53)
ISR Episodes[b]						
Total no. AEs	9	38	47	3	45	48
Rate per 100 PY (95% CI)	33.8 (15.47,64.23)	159.5 (112.85,218.88)	93.2 (68.48,123.93)	13.6 (2.80,39.71)	177.0 (129.07,236.78)	101.0 (74.49,133.95)

[a] All individual ISR symptoms are counted.
[b] Individual ISR symptoms are counted as a single ISR episode when presented simultaneously (i.e. same injection interval) at the same injection site.
Source WA28117: t_ae_rate_SE_ISR in WA28117 CSR; SPAAH175_rate_SE_ISR .
Source WA29231: t_ae_rate_SE_ISR and SPAAH175_rate_SE_ISR

Table 25 - Overview of injection site reactions episodes with TCZ SC in paediatric patients with pJIA (Studies WA28117 and WA29231) and adults patients with rheumatoid arthritis (Studies WA22762 and NA25220)

	pJIA		Adult RA	
	Study WA28117 (Week 52) All TCZ SC N = 52	LTE Study WA29231 (Cut-off July 2016) All TCZ SC LTE N = 41	Study WA22762 (Final CSR) 162 mg SC TCZ qw+DMARD N=631	Study NA25220 (Final CSR) 162 mg SC TCZ q2w+DMARD N=437
Duration in study (PY)	50.43	47.51	1013.26	404.34
No. pts (%)	15 (28.8%)	7 (17.1%)	77 (12.2%)	39 (8.9%)
Total no. AEs	47	48	264	89
Rate per 100 PY [95% CI]	93.2 [68.48,123.93]	101.0 [74.49,133.95]	26.1 [23.01, 29.39]	22.0 [17.68, 27.09]

CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IV = intravenous; PY = patient years; q2w = every two weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Duration in study = (date of last assessment - date of first dose + 1 day) / 365.25.

On the AE eCRF page, identify AE records that have a 'Yes' response for the 'Did the event occur at injection site?' tick box OR if there is a preferred term in the text field that is presently under the HLT 'Injection Site Reactions'

Multiple occurrences of the same adverse event in one individual are counted.

This output records individual ISR symptoms as a single ISR when presented simultaneously (i.e. same injection interval) in the same injection site.

Source WA28117: SPAAH175_rate_SE_ISR .

Source WA29231: SPAAH175_rate_SE_ISR.

Source WA22762: Table 37 in WA22762 Final CSR.

Source NA25220: Table 48 and slae05_isr in NA25220 Final CSR.

AEs occurred at the site of TCZ SC injection (ISRs) in 15/52 (28.8%) pJIA patients in Study WA28117 and in 7/41 (17.1%) pJIA patients in LTE Study WA29231.

With the exception of one non-serious Grade 2 event in LTE Study WA29231, all ISR events reported by pJIA patients treated with TCZ SC were non-serious Grade 1 events, and none required patient withdrawal from treatment or dose interruption.

The rate of ISR episodes per 100 PYs in Study WA28117 (93.2 [95% CI: 68.48,123.93]) was higher than the corresponding rates observed in adult RA patients treated with TCZ SC in Phase III studies WA22762 (26.1 [95% CI: 23.01, 29.39]) and NA25220 (22.0 [95% CI: 17.68, 27.09]).

Closer analysis of the WA28117 data show that approximately half of the 57 ISR events (30/57 events, 52.6%) were reported by three patients. All three patients were in the ≥ 30 kg BW group and were between 15 and 17 years of age.

Of the total 52 ISR events reported in LTE Study WA29231, 39 (75%) events were reported by two patients in the ≥ 30 kg BW group. Both patients were ADA negative post-baseline (measured at Weeks 24, 48, and 72).

Neutropenia adverse events

Table 26 - Rate of neutropenia AEs in pJIA patients treated with SC ((Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[b]
Duration in study (PY)	26.60	23.83	50.43	22.08	25.43	47.51	24.68	123.94	184.44
No. pts (%)	4 (14.8%)	1 (4.0%)	5 (9.6%)	3 (14.3%)	1 (5.0%)	4 (9.8%)	0	0	0
Total no. AEs	10	1	11	8	1	9	-	-	-
Rate per 100 PY (95% CI)	37.6 (18.03, 69.14)	4.2 (0.11, 23.38)	21.8 (10.89, 39.03)	36.2 (15.64, 71.39)	3.9 (0.10, 21.91)	18.9 (8.66, 35.96)	-	-	-

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

[a] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA19977 safety population including those in dose groups not shown.

Source WA28117: t_ae_rate_SE_NEUT_NOSPLT in WA28117 CSR.

Source WA29231: t_ae_rate_SE_NEUT

Source WA19977: Section 7.9.3 in 40-Week WA19977 CSR.

In Study WA28117, 5/52 (9.6%) pJIA patients experienced a total of 11 neutropenia AEs after receiving TCZ SC (Table 30, Table 31). Four of the 5 patients were in the < 30 kg BW group, and all patients were naive to TCZ.

All neutropenia AEs were deemed related to study treatment but none were reported as serious. Three of the 5 patients had dose interruptions as a result of their neutropenia AE. Two patients experienced infections within 30 days, preceding or following, a neutropenia AE:

One Patient (< 30 kg BW), who had a total of five reported neutropenia events, experienced three non-serious infections within 30 days of a reported neutropenia event: nasopharyngitis 27 days before the second neutropenia event, gastroenteritis 19 days before the second neutropenia event, and nasopharyngitis 7 days after the third neutropenia event.

One patient (< 30 kg BW), who had a total of three reported neutropenia events, experienced two non-serious infections within 30 days of a reported neutropenia event: nasopharyngitis 7 days after the first reported neutropenia event, and otitis media 25 days after the third reported neutropenia event

A total of 4/41 (9.6%) pJIA patients in Study WA29231 experienced a neutropenia AE after receiving TCZ SC. Two of the 4 patients had previously had a neutropenia event in Study WA28117. All neutropenia events in WA29231 were deemed related to study treatment but none were reported as serious.

Other adverse events of special interest

No events were identified in the pJIA TCZ SC studies for opportunistic infections, serious hepatic events, gastrointestinal perforations, demyelinating disorders, MI/acute coronary syndrome, stroke, serious bleeding, malignancies, and thrombocytopenia AEs.

Laboratory findings

Neutrophil count

Table 27 - Low neutrophil counts - Summary of worst NCI CTCAE Grade post-baseline in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

| | TCZ SC | | | | | | TCZ IV | | |
| | Study WA28117 (Week 52) | | | Study WA29231 (Cut-off July 2016) | | | Study WA19977 (Week 40)[a] | | |
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[b]
n	27	25	52	20	19	39	28	119	188
Neutrophil Counts									
Normal	16 (59.3%)	14 (56.0%)	30 (57.7%)	14 (70.0%)	11 (57.9%)	25 (64.1%)	21 (75.0%)	77 (64.7%)	129 (68.6%)
Grade 1	0	2 (8.0%)	2 (3.8%)	0	2 (10.5%)	2 (5.1%)	0	13 (10.9%)	14 (7.4%)
Grade 2	4 (14.8%)	8 (32.0%)	12 (23.1%)	2 (10.0%)	5 (26.3%)	7 (17.9%)	5 (17.9%)	27 (22.7%)	38 (20.2%)
Grade 3	7 (25.9%)	1 (4.0%)	8 (15.4%)	3 (15.0%)	1 (5.3%)	4 (10.3%)	2 (7.1%)	1 (0.8%)	6 (3.2%)
Grade 4	0	0	0	1 (5.0%)	0	1 (2.6%)	0	1 (0.8%)	1 (0.5%)
Grade ≥ 3	7 (25.9%)	1 (4.0%)	8 (15.4%)	4 (20.0%)	1 (5.3%)	5 (12.8%)	2 (7.1%)	2 (1.7%)	7 (3.7%)

IV = intravenous; LTE = long-term extension; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q2/3/4W = every 2/3/4 weeks; SC = subcutaneous; TCZ = tocilizumab.

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

[a] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA19977 safety population including those in dose groups not shown.

NCI CTCAE grading: Version 4.0 was used in studies WA28117 and WA29231; Version 3.0 was used in study WA19977.

Source WA28117: Table 17 in WA28117 CSR.

Source W29231: t_lb_shift_SE_HEM.

Source WA19977: Table 46 in Week 40 WA19977 CSR.

The majority of pJIA patients in Study WA28117 (57.7%) and LTE Study WA29231 (64.1%) maintained a neutrophil count within the normal range throughout treatment with TCZ SC.

The overall incidence of NCI-CTCAE Grade ≥ 3 post-baseline low neutrophil counts was 15.4% in TCZ SC Study WA28117 compared with 3.7% in TCZ IV Study WA19977. The incidence of Grade ≥ 3 post-baseline low neutrophil counts was higher in patients weighing <30 kg than in patients weighing ≥ 30 kg in TCZ SC Study WA28117 (25.9% vs. 4.0%), which is consistent with observations in TCZ IV Study WA19977 (7.1% vs. 1.7%). Most Grade 3 decreases in neutrophil counts in patients treated with TCZ SC were single occurrences. Patients who experienced Grade 3 low neutrophil count abnormalities in TCZ SC Study WA28117 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 TCZ SC Study WA28117. One patient had a Grade 4 low neutrophil count in LTE Study WA29231 (decreased from Grade 2 at baseline).

Table 28 - Patients with an infection AE within 30 days of a Grade $\geq$ 1 low neutrophil count (Study WA29231, safety population)

BW Group	Age (years)/ Sex	Low Neutrophil Count [a] (Study Day)	Infection Preferred Term (Study Day)	Serious	Days within Low Neutrophil Count [b]
<30 kg	7/F	1.1 (503)	Respiratory tract infection (485)	No	-18
<30 kg	3/F	1.0 (149)	Gastroenteritis (141)	No	+8
		0.6 (211)[d]	Gastroenteritis (239)	No	-28
		1.0 (380)	Nasopharyngitis (358)	No	+22
<30 kg	6/F	0.8 (169)[d]	Otitis media (158)	No	+11
		1.0 (547)	Gastroenteritis (534)	No	+13
$\geq$ 30 kg	18/F	1.3 (87)	Nasopharyngitis (78)	No	+9
		1.8 (452)	Nasopharyngitis (427)	No	+25
$\geq$ 30 kg	14/M	1.3 (75)	Influenza (105)	No	-30

BW = body weight; F = female; M = male.

a Total absolute neutrophil count (10^9/L).

b Infections within 30 days, preceding (marked with minus) or following (marked with plus), the patient's low neutrophil counts.

c Experienced an infection within 30 days, preceding or following, a low neutrophil count in Study WA28117.

d CTC Grade 3 low neutrophil count.

No serious infection AEs occurred in TCZ SC Study WA28117 within 30 days preceding or following a low neutrophil count (of any grade).

Platelet Counts

Table 29 - Low platelet counts - Summary of worst NCI CTCAE Grade post-Baseline in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

	TCZ SC						TCZ IV		
	Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 40)[a]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188 [b]
n	27	25	52	20	19	39	28	119	188
Normal	24 (88.9%)	24 (96.0%)	48 (92.3%)	18 (90.0%)	18 (94.7%)	36 (92.3%)	23 (82.1%)	110 (92.4%)	172 (91.5%)
Grade 1	3 (11.1%)	1 (4.0%)	4 (7.7%)	1 (5.0%)	1 (5.3%)	2 (5.1%)	4 (14.3%)	7 (5.9%)	13 (6.9%)
Grade 2	0	0	0	0	0	0	0	1 (0.8%)	1 (0.5%)
Grade 3	0	0	0	0	0	0	1 (3.6%)	0	1 (0.5%)
Grade 4	0	0	0	1 (5.0%)	0	1 (2.6%)	0	1 (0.8%)	1 (0.5%)
Grade ≥ 3	0	0	0	1 (5.0%)	0	1 (2.6%)	1 (3.6%)	1 (0.8%)	2 (1.1%)

IV = intravenous; LTE = long-term extension; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.

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

[a] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA19977 safety population including those in dose groups not shown.

NCI CTCAE grading: Version 4.0 was used in studies WA28117 and WA29231; Version 3.0 was used in study WA19977.

Source WA28117: Table 21 in WA28117 CSR.

Source WA29231: t_lb_shift_SE_HEM.

Source WA19977: Table 49 in Week 40 WA19977 CSR.

Most pJIA patients in Study WA28117 (92.3%) and LTE Study WA29231 (92.3%) maintained a platelet count within the normal range throughout treatment with TCZ SC.

With the exception of one Grade 4 low platelet count in LTE Study WA29231, all low platelet count abnormalities in TCZ SC Studies WA28117 and WA29231 were Grade 1.

There was no correlation between low platelet counts and serious bleeding events, and no thrombocytopenia AEs were reported, in either Study WA28117 or WA29231.

Liver enzymes

Table 30 - Liver function test Elevations - summary of highest NCI CTCAE grade post-baseline in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

| | TCZ SC | | | | | | TCZ IV | | |
| | Study WA28117 (Week 52) | | | Study WA29231 (Cut-off July 2016) | | | Study WA19977 (Week 40)[a] | | |
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188 [b]
n	27	25	52	20	19	39	28	119	187
ALT									
Normal	14 (51.9%)	18 (72.0%)	32 (61.5%)	16 (80.0%)	14 (73.7%)	30 (76.9%)	25 (89.3%)	70 (58.8%)	126 (67.4%)
Grade 1	10 (37.0%)	5 (20.0%)	15 (28.8%)	4 (20.0%)	5 (26.3%)	9 (23.1%)	2 (7.1%)	41 (34.5%)	52 (27.8%)
Grade 2	2 (7.4%)	1 (4.0%)	3 (5.8%)	0	0	0	1 (3.6%)	7 (5.9%)	8 (4.3%)
Grade 3	1 (3.7%)	1 (4.0%)	2 (3.8%)	0	0	0	0	1 (0.8%)	1 (0.5%)
Grade 4	0	0	0	0	0	0	0	0	0
Grade ≥ 2 [c]	3 (11.1%)	2 (8.0%)	5 (9.6%)	0	0	0	1 (3.6%)	8 (6.7%)	9 (4.8%)
AST									
Normal	18 (66.7%)	21 (84.0%)	39 (75.0%)	17 (85.0%)	18 (94.7%)	35 (92.3%)	25 (89.3%)	92 (77.3%)	152 (81.3%)
Grade 1	8 (29.6%)	3 (12.0%)	11 (21.2%)	3 (15.0%)	1 (5.3%)	4 (10.3%)	2 (7.1%)	25 (21.0%)	32 (17.1%)
Grade 2	0	0	0	0	0	0	1 (3.6%)	1 (0.8%)	2 (1.1%)
Grade 3	1 (3.7%)	1 (4.0%)	2 (3.8%)	0	0	0	0	1 (0.8%)	1 (0.5%)
Grade 4	0	0	0	0	0	0	0	0	0
Grade ≥ 2 [c]	1 (3.7%)	1 (4.0%)	2 (3.8%)	0	0	0	1 (3.6%)	2 (1.7%)	3 (1.6%)

| | TCZ SC | | | | | | TCZ IV | | |
| | Study WA28117 (Week 52) | | | Study WA29231 (Cut-off July 2016) | | | Study WA19977 (Week 40)[a] | | |
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 28	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188 [b]
n	27	25	52	20	19	39	28	119	187
Total bilirubin									
Normal	26 (96.3%)	22 (88.0%)	48 (92.3%)	17 (85.0%)	16 (84.2%)	33 (84.6%)	25 (89.3%)	100 (84.0%)	160 (85.6%)
Grade 1	1 (3.7%)	3 (12.0%)	4 (7.7%)	3 (15.0%)	1 (5.3%)	4 (10.3%)	1 (3.6%)	9 (7.6%)	14 (7.5%)
Grade 2	0	0	0	0	2 (10.5%)	2 (5.1%)	2 (7.1%)	10 (8.4%)	13 (7.0%)
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	0	0	0	2 (10.5%)	2 (5.1%)	2 (7.1%)	10 (8.4%)	13 (7.0%)

IV = intravenous; LTE = long-term extension; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.

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

[a] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.

[b] The 'All TCZ IV' group includes all patients in the WA19977 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 WA28117 and WA29231 (CTCAE version 4.0) and > 2.5x ULN in Study WA19977 (CTCAE version 3.0). See Table 5.

NCI CTCAE grading: Version 4.0 was used in studies WA28117 and WA29231; Version 3.0 was used in study WA19977.

Source WA28117: Table 22 in WA28117 CSR.

Source W29231: t_lb_shift_SE_LIVER.

Source WA19977: Tables 50, 51, and 52 in Week 40 WA19977 CSR.

No patients met the laboratory criteria for Hy's Law in TCZ SC Studies WA28117 or WA29231 and there were no serious hepatic events or Grade 4 elevations in ALT, AST, or bilirubin concentrations.

The laboratory profiles for ALT, AST and bilirubin in TCZ SC Study WA28117 were comparable in the two BW groups (< 30 kg vs. ≥ 30 kg); the majority of patients had ALT, AST, and bilirubin values within the normal range throughout TCZ SC treatment.

Grade $\geq$ 2 elevations were seen in 9.6% patients for ALT and 3.8% patients for AST in TCZ SC Study WA28117 compared with 4.8% and 1.6% of patients, respectively, in TCZ IV Study WA19977. No Grade $\geq$ 2 elevations in ALT or AST were reported in TCZ SC LTE Study WA29231 up to the clinical cut-off.

Lipid parameters

Table 31 - Total and LDL Cholesterol - Summary of post-baseline elevations in pJIA patients treated with SC (Studies WA28117 and WA29231) or IV (Study WA19977) TCZ (safety populations)

		TCZ SC					TCZ IV		
		Study WA28117 (Week 52)			Study WA29231 (Cut-off July 2016)			Study WA19977 (Week 104)[a, b]		
	TCZ SC Q3W (< 30 kg) N = 27	TCZ SC Q2W (≥ 30 kg) N = 25	All TCZ SC N = 52	TCZ SC Q3W (< 30 kg) N = 21	TCZ SC Q2W (≥ 30 kg) N = 20	All TCZ SC LTE N = 41	10 mg/kg Q4W (< 30 kg) N = 22	8 mg/kg Q4W (≥ 30 kg) N = 119	All TCZ IV N = 188[c]
n	26[d]	25	51	10	18	28	22	117	185
Total ≥ 200 mg/dL	1 (3.8%)	9 (36.0%)	10 (19.6%)	1 (10.0%)	6 (33.3%)	7 (25.0%)	2 (9.1%)	17 (14.5%)	22 (11.9%)
LDL ≥ 130 mg/dL	1 (3.8%)	8 (32.0%)	9 (17.6%)	1 (10.0%)	4 (22.2%)	5 (17.9%)	1 (4.5%)	7 (6.0%)	10 (5.4%)

IV = intravenous; LDL = low density lipoprotein; LTE = long-term extension; Q2/3/4W = every 2/3/4 weeks; SC = subcutaneous; TCZ = tocilizumab.
Includes patients with an elevation at baseline.
Percentages are based on n (number of valid values).
Patients were fasted for a minimum of 8 hours before sampling.
[a] Data from the 104-Week WA19977 CSR are used for this analysis because corresponding data are not available in the 40-Week WA19977 CSR.
[b] Data on placebo treatment received in Part II (withdrawal phase) of study WA19977 are excluded.
[c] The 'All TCZ IV' group includes all patients in the WA19977 safety population including those in dose groups not shown.
[d] Lipid data are not available for TCZ naive patient 271769/117005.
Source WA28117: t_lb_elev_SE in the WA28117 CSR.
Source WA29231: t_lb_elev_SE.
Source WA19977: stdm11_elv_cho and stdm1_elv_ldl in the 104-Week WA19977 CSR.

The majority of pJIA patients had total and LDL cholesterol levels below the elevated concentration cut points of $\geq$ 200 mg/dL for total cholesterol (fasted) and $\geq$ 130 mg/dL for LDL-cholesterol (fasted) throughout treatment with TCZ SC (WA28117: 80.4% and 82.4%, respectively; LTE WA29231: 75.0% and 82.1%, respectively).

Excluding patients with elevations at baseline, the percentage of patients with a newly occurring post-baseline elevation in total cholesterol to $\geq$ 200 mg/dL was similar in Studies WA28117 and WA19977 (6/47 patients [12.8%] vs. 19/182 patients [10.4%], respectively). Excluding patients with elevations at baseline, the percentage of patients with a newly occurring post-baseline elevation in LDL cholesterol to $\geq$ 130 mg/dL was higher in WA28117 than in WA19977 (14.3% [7/49 patients]) vs. 3.4% [6/179 patients], respectively). However, as treatment with TCZ has previously been shown to be associated with increases in lipid parameters, it should be noted that 4 of the 7 patients in WA28117 had previously received TCZ IV; looking only at TCZ naive patients in WA28117, the proportion of patients with a newly occurring post-baseline elevation in LDL cholesterol was 8.3% (3/36 TCZ naïve patients).

In LTE Study WA29231, 7/28 (25.0%) patients had a post-baseline elevation of total cholesterol to $\geq$200 mg/dL and 5/28 (17.9%) patients had a post-baseline elevation of LDL cholesterol to $\geq$ 130 mg/dL. All patients in LTE Study WA29231 with a post-baseline elevation in total and/or LDL cholesterol had previously had an elevation in Study WA28117.

No hyperlipidaemia AEs or serious cardiovascular events were reported in the TCZ SC studies.

Safety in special populations

Intrinsic factors

As part of the WA28117, WA29231, and WA19977 study designs, two dosing regimens based on BW (< 30 kg and ≥ 30 kg) were used. Safety result comparisons between the two BW groups are made as appropriate in other sections.

No other safety analyses based on intrinsic factors were performed for Studies WA28117 or WA29231 due to the small patient numbers.

Safety related to drug-drug interactions and other interactions

No new data on drug interactions are available or needed.

Discontinuation due to adverse events

There were no patients in Study WA28117 who experienced an AE that led to withdrawal of TCZ SC treatment.

One patient experienced an AE that led to withdrawal of TCZ SC treatment in LTE Study WA29231 prior to the clinical cut-off. The event was reported as Grade 2 juvenile idiopathic arthritis, which indicates that the reason for discontinuing treatment in this patient was insufficient efficacy.

One additional patient experienced an AE that led to withdrawal of TCZ SC treatment in LTE study WA29231 after the clinical cut-off. The patient in the <30 kg BW group was withdrawn due to an AE of neutropenia; the patient had multiple Grade 3 low neutrophil count laboratory abnormalities during the course of Studies WA28117 and WA29231

The incidence of patients experiencing AEs that led to dose interruption in WA28117 (11.5% [6/52]) was comparable with the incidence observed in the All TCZ IV Week 40 population of Study WA19977 (12.8% [24/188]) and the LTE Study WA29231 (17.1% [7/41]).

2.5.1. Discussion on clinical safety

The main study contributing to the safety evaluation of TCZ SC in pJIA is the 52-week randomized open-label Phase 1b pharmacokinetic (PK)/ pharmacodynamic (PD) bridging Study WA28117. The safety analyses are based on final data from 52 pJIA patients who received TCZ SC for a total duration of 50.43 patient years (PY). The final TCZ SC safety data from Study WA28117 are compared with intravenous (IV) TCZ safety data from Study WA19977, the pivotal Phase III study for the approval of the IV formulation of TCZ in pJIA patients in 2013 (184.44 PY)

Supportive data on the long-term safety of TCZ SC in patients with pJIA are provided from 41 pJIA patients in Study WA29231, the ongoing open-lab long-term extension (LTE) of Study WA28117. The analyses are based on data collected up to a clinical cut-off date of 17 July 2016, which contribute an additional duration of 47.51 PYs.

The overall rate of AEs in pJIA patients who received TCZ SC in Study WA28117 (805.1 [95% CI: 728.66, 887.33] AEs per 100 PY) was higher than the rate observed in the All TCZ IV Week 40 population of Study WA19977 (479.8 [95% CI: 448.73, 512.51] AEs per 100 PY). The higher overall AE rate in TCZ SC Study WA28117 was partly due to a higher rate of ISRs related to the SC mode of administration. Excluding the 57 ISR AEs, the overall AE rate for WA28117 is 692.0 [95% CI: 621.34, 768.60] AEs per 100 PY.

The overall rate of AEs in LTE Study WA29231 (585.1 [95% CI: 518.37, 658.12] AEs per 100 PY) was lower than the rate in Study WA28117, indicating a declining trend in the rate of AEs over time in pJIA patients receiving TCZ SC.

Analysis of the WA28117 data by body weight group showed a higher AE rate in patients in the > 30 kg BW group compared with patients in the < 30 kg BW group (944.2 [95%CI: 824.84, 1075.96] vs. 680.5 [584.93, 787.13], respectively).

The higher overall AE rate in patients weighing > 30 kg was primarily driven by higher AE rates in the Musculoskeletal and Connective Tissue Disorders (mostly arthralgia, pain in extremity, and joint swelling), Gastrointestinal Disorders (mostly nausea), General Disorders and Administration Site Conditions (mostly ISR-related AEs and Nervous System Disorders (mostly headache) SOCs. Conversely, higher AE rates were observed in patients in the < 30 kg BW group compared with patients in the > 30 kg BW group in the Infections and Infestations (mostly nasopharyngitis and gastroenteritis and Blood and Lymphatic System Disorders.

At the time of the clinical cut-off (17 July 2016), 34/41 (82.9%) pJIA patients in LTE Study WA29231 had experienced a total of 278 AEs; 17/21 (81.0%) patients in the < 30 kg BW group and 17/20 (85.0%) patients in the > 30 kg BW group. The overall AE rate was similar in the two BW subgroups. Consistent with results in Study WA28117, SOCs with a notably higher AE rate in patients in the > 30 kg BW group were Musculoskeletal and Connective Tissue Disorders (mostly arthralgia) and General Disorders and Administration Site Conditions (mostly ISR-related AEs), whereas SOCs with a notably higher AE rate in the < 30 kg BW group were Infections and Infestations (mostly due to differences in rates of gastroenteritis and ear infection) and Blood and Lymphatic System Disorders (mostly neutropenia).

No deaths were reported in TCZ SC Studies WA28117 and WA29231 or in TCZ IV Study WA19977.

The rate of SAEs in the WA28117 All TCZ SC population (7.9 [95% CI: 2.16, 20.31] SAEs per 100 PY) was comparable with the rate in the WA19977 All TCZ IV Week 40 population (12.5 [95% CI: 7.91, 18.71] SAEs per 100 PY) indicating no increase in the rate of SAEs with the SC regimen compared with the IV regimen.

In LTE Study WA29231 the SAE rate based on the 4 events was 8.4 [95% CI: 2.29, 21.56] SAEs per 100 PY.

For several of the pre-specified AESI categories i.e opportunistic infections, serious hepatic events, gastrointestinal perforations, demyelinating disorders, MI/acute coronary syndrome, stroke, serious

There was no increase in the rate of infection when comparing between the SC and IV regimens (WA28117 All TCZ SC: 168.6 [95% CI 134.63, 208.42] AEs per 100 PY vs. WA19977 All TCZ IV Week 40: 163.7 [95% CI: 145.79, 183.29] AEs per 100 PY). Additionally, the rate of infection AEs in the WA29231 All TCZ SC LTE safety population (136.8 [95% CI: 105.59, 174.38]) showed no increase in the rate of infection AEs over time in pJIA patients receiving TCZ SC.

No anaphylactic reactions occurred in either the pJIA TCZ SC program or in the TCZ IV Study WA19977 (40-Week WA19977 CSR). One patient was identified in Study WA28117 as having non-serious Grade 1 signs and symptoms of a potential anaphylactic reaction according to Sampson's criteria; however it was considered that it did not represent a systemic anaphylactic reaction.

Neutropenia AEs were reported by 5/52 (9.6%) pJIA patients in Study WA28117 and by 4/41 (9.6%) patients in LTE Study WA29231 following TCZ SC treatment compared with no patients reporting a neutropenia AE in the All TCZ IV Week 40 population (40-Week WA19977 CSR); however, 3/188 (1.6%) patients in the All TCZ IV Week 104 population experienced a neutropenia AE (104-Week WA19977 CSR). In LTE Study WA29231, 2 of the 4 patients previously had a neutropenia AE in WA28117. None of the

neutropenia events were reported as serious or associated with a serious infection within 30 days of the neutropenia AE.

The majority of pJIA patients in Study WA28117 (57.7%) and LTE Study WA29231 (64.1%) maintained a neutrophil count within the normal range throughout treatment with TCZ SC, which is in line with the All TCZ IV Week 40 population of Study WA19977 (68.6%). However, a higher overall incidence of Grade > 3 low neutrophil counts was observed in TCZ SC Study WA28117 (15.4%, almost all patients were TCZ naive) compared with that in TCZ IV Study WA19977 (3.7%), with a greater proportion of patients weighing < 30 kg having Grade > 3 low neutrophil counts than patients weighing >30 kg in TCZ SC Study WA28117 (25.9% vs. 4.0%); this BW trend in Grade > 3 low neutrophil counts is, however, consistent with observations in the TCZ IV Study WA19977 (< 30 kg: 7.1% vs. > 30 kg: 1.7%).

Most pJIA patients in Study WA28117 (92.3%) and LTE Study WA29231 (92.3%) maintained a platelet count within the normal range throughout treatment with TCZ SC, which is consistent that observed in the All TCZ IV Week 40 population of Study WA19977 (91.5%).

The majority of pJIA patients had ALT, AST, and total bilirubin concentrations within the normal range throughout treatment with TCZ SC (WA28117: 61.5%, 75.0%, and 92.3%; WA29231: 76.9%, 92.3%, and 84.6%, respectively), which is consistent with that observed in the TCZ IV Study WA19977 (67.4%, 81.3%, and 85.6%, respectively).

The majority of pJIA patients had total cholesterol 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) (Daniels et al. 2008) throughout treatment with TCZ SC (WA28117: 80% and 82%, respectively; LTE WA29231: 75% and 82%, respectively).

2.5.2. Conclusions on clinical safety

A robust safety analysis is hampered by the small, sample size and relative short exposure for the TCZ SC patients (50.43 PY). However the safety profile of TCZ is well established in patients with pJIA (see AR variation II/26).

The overall rate of AEs in pJIA patients who received TCZ SC in Study WA28117 was higher than the overall rate observed in the pJIA patients in TCZ IV Study WA19977, however, the overall rate of AEs in LTE Study WA29231 was lower than in WA28117. The higher AE rate in Study WA28117 was due in part to the occurrence of ISRs related to the SC mode of administration.

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

Data on exposure safety-relationship were provided. Overall, data and analyses showed a slight exposure response relationship regarding safety with more adverse events and lower blood cell counts in especially the very light patients. Although there were limited numbers of patients in the two body weight extremes, trends but no clear correlation between TCZ exposure-response relationships could be detected that manifest a clinically significant safety or efficacy concern associated with the extremes of body weight. In some patients factors other than weight alone may contribute to poor responses or safety concerns.

No new safety concerns were identified.

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 23.1 is acceptable.

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 23.1 with the following content:

Safety concerns

Summary of Ongoing Safety Concerns in Adults

Category	Safety Concern
Important Identified Risks	Serious infections
	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	Elderly patients
	Pediatric patients
	Effects during pregnancy
	Hepatic impairment
	Renal impairment
	Combination with biologics
	Safety in patients <60 kg in switcher population
	Long-term safety in patients in the switcher patient population
Identified and potential interactions including food-drug and drug-drug interactions	CYP450 enzyme normalization

Summary of Ongoing Safety Concerns in Paediatric Patients

Category	Safety Concern
Important Identified Risks	Serious infections
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Skeletal development
	Immunogenicity
	Malignancies
	CYP450 enzyme normalization
Missing information	MAS in sJIA patients

Pharmacovigilance plan

Activity/Study title (category 3)*	Objectives	Safety concerns addressed	Status Planned, started, ongoing	Date for submission of interim or final reports (planned or actual)
WA22479 (British Society of Rheumatology Biologics Register [BSRBR])	Prospective observational cohort studies for safety data collection.	General safety profile of TCZ. Safety of TCZ SC in patients < 60 kg in the switcher population. Long-term safety in switcher patient population.	Ongoing	Routine updates to be provided in the scheduled PSURs. Final CSR Q3 2017
WA22480 (ARTIS) registry study	To provide long term safety data from the use of TCZ in Sweden for RA patients			Routine updates to be provided in the scheduled PSURs. Final CSR Q4 2019
GA28719 (RABBIT)	The long-term observation of treatment with biologics in RA (RABBIT) in German biologics registry			Routine updates to be provided in the scheduled PSURs. Final CSR Q4 2018
Pregnancy registry (GA28720 [OTIS])	To evaluate pregnancy outcomes for women exposed to TCZ during pregnancy			Routine updates to be provided in the scheduled PSURs. Final CSR Q4 2019
Paediatric Registry	Collecting long term efficacy	Safety in pediatric	Ongoing	Final report date

Activity/Study title (category 3)*	Objectives	Safety concerns addressed	Status Planned, started, ongoing	Date for submission of interim or final reports (planned or actual)
(WA29358): Observational Safety and Effectiveness Study of Patients with Polyarticular Juvenile Idiopathic Arthritis Treated with Tocilizumab	and safety data in PJIA treatment. The registry will address, but is not limited to, efficacy of 10 mg/kg for patients < 30 kg; impact of the RF status on efficacy of TCZ therapy; impact of TCZ therapy on the increased risk of atherosclerosis in RA patients, impact on of TCZ therapy growth development, influence on the occurrence / treatment of uveitis. and to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation	patients		expected March 2025.
WA28029	To evaluate decreased dose frequency in patients with sJIA who experience laboratory abnormalities during treatment with TCZ	Safety in pediatric patients	Ongoing	First Patient First Visit June 2013 Final CSR expected 2020
NP25737	A pharmacokinetic and safety study of TCZ in patients less than 2 years old with active sJIA	Safety profile in pediatric patients less than 2 years old	Ongoing	Final CSR expected November 2017

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important Identified Risks		

Serious Infections	SPC
	    Section 4.3 Contraindications
	    Section 4.4 Special warnings and precautions for use
	    Section 4.8 Undesirable effects
	Patient Information Leaflet
	    Section 2, Warnings and precautions
	    Section 4 Possible side effects
		Patient Alert Card;
		Patient Brochure;
		Healthcare Provider Brochure

Complications of diverticulitis	SPC
	    Section 4.4 Special warnings and precautions for use
	    Section 4.8 Undesirable effects
	Patient Information Leaflet
	    Section 2, Warnings and precautions
	    Section 4 Possible side effects
		Patient Alert Card;
		Patient Brochure;
		Healthcare Provider Brochure

Serious Hypersensitivity Reactions	SPC
	    Section 4.3 Contraindications
	    Section 4.4 Special warnings and precautions for use
		Patient Alert Card;
		Patient Brochure;

Safety concern	Routine risk minimization measures	Additional risk minimization measures

	Section 4.8 Undesirable effects
	Patient Information Leaflet
	    Section 2, Warnings and precautions
	    Section 4 Possible side effects
		Healthcare Provider Brochure;
		
		Rheumatoid Arthritis Dosing Guide

Neutropenia	SPC
	    Section 4.2 Posology and method of administration
	    Section 4.4 Special warnings and precautions for use
	    Section 4.8 Undesirable effects/Laboratory evaluations
	Patient Information Leaflet
	    Section 4 Possible side effects
		Patient Brochure;
		
		Healthcare Provider Brochure

Important Potential Risks		

Thrombocytopenia and the potential risk of bleeding	SPC
	    Section 4.2 Posology and method of administration
	    Section 4.4 Special warnings and precautions for use
	    Section 4.8 Undesirable effects
		Patient Brochure;
		
		Healthcare Provider Brochure

Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity	SPC
	    Section 4.2 Posology and method of administration
	    Section 4.4 Special warnings and precautions for use
	    Section 4.8 Undesirable effects
	Patient Information Leaflet
	    Section 2, Warnings and precautions
		Patient Brochure;
		
		Healthcare Provider Brochure

Elevated Lipid Levels and Potential Risk of Cardiovascular/ Cerebrovascular Events	SPC
	    Section 4.4 Special warnings and precautions for use
	    Section 4.8 Undesirable effects
	Patient Information Leaflet
	    Section 2 Warnings and precautions
		Patient Brochure;
		
		Healthcare Provider Brochure

Malignancies	SPC
	    Section 4.4 Special warnings and precautions for use
	    Section 4.8 Undesirable effects
		Patient Brochure;
		
		Healthcare Provider Brochure

Demyelinating disorders	SPC Section 4.4 Special warnings and precautions for use	Healthcare Provider Brochure
Immunogenicity	SPC Section 4.8. Undesirable effects	None proposed
Skeletal development (in paediatric patients)	None proposed	Not applicable
Missing Information		

CYP450 enzyme normalization	SPC
	    Section 4.5 Interaction with other medicinal products and other forms of interaction
	Patient Information Leaflet
	    Section 2, Other medicines and RoActemra
		None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures

Macrophage Activation Syndrome in sJIA Patients	SPC
	        Section 4.4 Special warnings and precautions for use
	Patient Information Leaflet
	        Section 2, Children and adolescents
		Patient Alert Card

Pediatric patients	SPC
	        Section 4.2 Posology and method of administration
	        Section 4.4 Special warnings and precautions for use
	        Section 4.5: Interactions with other medicinal products
	Patient Information Leaflet
	        Section 1 What RoActemra is and what it is used for
	        Section 2, Children and adolescents
	        Section 4 Possible side effects
		None proposed

Elderly Patients	SPC Section 4.2 Posology and Method of Administration	None proposed

Effects during pregnancy	SPC
	        Section 4.6 Fertility, Pregnancy and lactation
	Patient Information Leaflet
	        Section 2, Pregnancy, breast feeding and fertility
		None proposed

Hepatic impairment	SPC
	        Section 4.2 Posology and Method of Administration.
	        Section 4.4 Special warnings and precautions for use
	        Section 5.2 Pharmacokinetic properties
	Patient Information Leaflet
	        Section 2, Warnings and precautions
		None proposed

Renal Impairment	SPC
	        Section 4.2 Posology and Method of Administration
	        Section 5.2 Pharmacokinetic properties
	Patient Information Leaflet
	        Section 2, Warnings and precautions
		None proposed

Combination with biologics	SPC
	        Section 4.4 Special warnings and precautions for use
	Patient Information Leaflet
	        Section 2, Other medicines and RoActemra
		None proposed

Safety in patients <60 kg in switcher population	SPC Section 5.1 Pharmacodynamic properties	None proposed
Long-term safety in the switcher patient population	SPC Section 5.1 Pharmacodynamic properties	None proposed

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to RoActemra 162 mg solution for subcutaneous injection in a pre-filled syringe. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application provides data to support the license extension of the TCZ SC formulation (delivered via a PFS + NSD) in pJIA as a fixed dose of 162 mg once every 3 weeks (Q3W) for patients weighing < 30 kg and once every 2 weeks (Q2W) for patients weighing ≥ 30 kg. TCZ IV has already been demonstrated to be a safe and efficacious treatment for patients with pJIA in Study WA19977.

3.1.2. Available therapies and unmet medical need

The development of TCZ SC as an alternative to TCZ IV in pJIA is desirable because 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 pJIA 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.

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 WA28117 (JIGSAW 117), which was designed to confirm the TCZ SC dosing regimens (selected using modelling and simulation) in patients aged 1 to 17 years old with pJIA, as well as to assess the safety of the TCZ SC formulation (efficacy was exploratory)

- Supportive data from the completed pivotal TCZ IV Study WA19977 (CHERISH), which led to approval of TCZ IV in pJIA;

- Supportive data from the ongoing, long-term extension (LTE) Study WA29231 (clinical cut-off date 17 July 2016), which is an open-label extension of the JIGSAW studies (WA28117 [pJIA] and WA28118 [sJIA]) with the aim to assess the long-term safety and efficacy of TCZ SC in pJIA and sJIA; and

- Supportive data (i.e., injection site reactions [ISRs and PK]) from the completed pivotal Phase III TCZ SC Studies WA22762 (SUMMACTA) and NA25220 (BREVACTA), which led to approval of TCZ SC in adult RA.

3.2. Favourable effects

Comparative efficacy, comparing TCZ naïve patients through Week 52 from Study WA28117 (SC treatment) with TCZ IV efficacy data from the "continuous TCZ" IV subgroup through Week 52 from Study WA19977, was shown (JADAS-71, clinical remission, inactive disease and CHAQ-DI score).

Overall normal growth patterns were observed after 1 year of TCZ treatment for both the TCZ studies.

3.3. Uncertainties and limitations about favourable effects

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance (see section 3.7. Benefit-risk assessment and discussion).

3.4. Unfavourable effects

The unfavourable effects of TCZ are established and include infection, allergic reactions including anaphylaxis, neutropenia, and thrombocytopenia, AST/ALT/bilirubin elevation and hypercholesterolaemia.

The higher AE rate in Study WA28117 was observed, due in part to the occurrence of ISRs related to the SC mode of administration

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

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance (see section 3.7. Benefit-risk assessment and discussion).

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

TCZ IV is now a well-established treatment option for patients with pJIA. 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 pJIA 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.

3.7.2. Balance of benefits and risks

The benefit-risk balance of TCZ IV was considered previously positive. TCZ SC shows an efficacy and safety profile comparable to the i.v. formulation while having the advantage of the more patient friendly administration.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit-risk 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 changes:

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 to include "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 methotrexate" for RoActemra; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics. The Package Leaflet is updated accordingly. The Risk Management Plan version 23.1 is adopted.

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

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.