NDA/BLA Multidisciplinary Review and Evaluation

Application Type	Supplement
Application Number(s)	125472/s31
Priority or Standard	Priority
Submit Date(s)	March 12, 2018
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PDUFA Goal Date	September 12, 2018
Division/Office	DPARP/ODEII
Review Completion Date	Stamp Date
Established Name	Tocilizumab
(Proposed) Trade Name	Actemra
Pharmacologic Class	IL-6 R Antagonist
Applicant	Genentech, Inc.
Formulation(s)	Subcutaneous
Dosing Regimen	• sJIA patients ≥ 30 kg 162 mg SC once every week • sJIA patients < 30 kg 162 mg SC once every two weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Patients ≥ 2 years with active sJIA

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CS	corticosteroid
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMARD	disease modifying anti-rheumatic drug
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAID	nonsteroidal anti-inflammatory drug
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
sJIA	systemic Juvenile Idiopathic Arthritis
SOC	standard of care
TCZ	tocilizumab
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Genentech submitted supplement 031 to BLA 125276 for subcutaneous tocilizumab (TCZ) for the treatment of systemic juvenile idiopathic arthritis (sJIA) in patients (b) (4). TCZ is a recombinant humanized anti-human interleukin 6 receptor (IL-6R) monoclonal antibody of the immunoglobulin IgG1 subtype with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively, and the four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. TCZ binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and competitively inhibits IL-6-mediated signaling through these receptors. IL-6 is a pleitropic pro-inflammatory cytokine produced by a variety of cell types including T and B lymphocytes, monocytes, and fibroblasts.

TCZ is available in intravenous (IV) and subcutaneous (SC) presentations. IV TCZ is supplied in single-use vials containing 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL of TCZ in an aqueous solution of disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate, polysorbate 80, and sucrose. SC TCZ is supplied in a 1.0 mL single-use prefilled syringe with a needle safety device that delivers 0.9 mL (162 mg) of TCZ in a histidine buffered solution of TCZ (180 mg/mL), polysorbate 80, L-histidine and L-histidine monohydrochloride, L-arginine and L-arginine hydrochloride, L-methionine, and water for injection.

TCZ was first approved in its IV formulation for the treatment of moderate to severely active rheumatoid arthritis (RA) on January 8, 2010. Since that time, IV TCZ has been approved for sJIA patients 2 years of age and older, polyarticular juvenile idiopathic arthritis (pJIA) patients 2 years of age and older, and cytokine release syndrome (CRS) patients 2 years of age and older. SC TCZ is approved for moderate to severely active RA, giant cell arteritis (GCA), and pJIA patients 2 years of age and older.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The basis for a regulatory action on this supplemental BLA is comparable exposure and extrapolation of established efficacy and safety of IV TCZ in patients with sJIA 2 years of age and older from Study WA18221 (the pivotal study supporting the approval of IV TCZ in this patient population, reviewed under BLA 125276). The study supporting this supplemental BLA, WA28118, was a phase 1b, 52-week, open-label, multicenter, PK/PD, and safety study in 51 pediatric patients with sJIA, aged 1 to 17 years-old to identify the SC dose regimen(s) with comparable PK/PD and safety profiles to the IV regimens established in study WA18221. Subjects were allowed treatment with disease-modifying anti-rheumatic drugs (DMARDs), NSAIDs, and oral corticosteroids during the study at the discretion of the investigator. Other immunosuppressants (e.g., cyclosporine, cyclophosphamide, and biologic DMARDs [TNFα

inhibitors and abatacept]) were not permitted. Initial dosing regimen was 162mg SC every week (QW) for subjects weighing ≥30 kg, and 162mg SC every 10 days (Q10D) for subjects weighing <30 kg. Following a pre-specified interim analysis, the dosing regimen for subjects weighing <30 kg was changed from Q10D to every 2 weeks (Q2W); the QW dosing regimen for subjects weighing ≥30 kg remained unchanged. The protocol allowed for adjustment of the TCZ dosing interval if there were any changes in the body weight (BW) after Week 14.

The PK parameters observed in sJIA patients treated with SC TCZ in Study WA28118 were within the range of exposures seen in sJIA patients treated with IV TCZ in WA18221. Specifically, Study WA28118 met its primary PK endpoint with steady state Cmin in each body weight group comparable to the Cmin achieved in the corresponding body weight group upon IV administration in study WA18221. As noted in the Clinical Pharmacology review, the median AUCs were approximately 30% lower with the SC TCZ compared to the IV TCZ program in sJIA. However, the applicant provided adequate justification, based on the exposure-response analyses from the IV TCZ program in sJIA, that this PK parameter was not relevant for the PK bridging strategy. The steady state AUCs following SC regimens were within the range of the IV regimens in sJIA patients. Further, differences in AUC are not clinically relevant given the flat exposure-efficacy relationship in the IV TCZ program in sJIA patients (study WA18221). Thus, the Clinical Pharmacology review team concluded that the 30% lower AUC is unlikely to result in compromised efficacy following SC administration compared to IV regimens. Exploratory efficacy assessments in WA28118 were consistent with improvement with treatment with SC TCZ. Based on the information in this supplement, the clinical pharmacology review team concluded, and I agree, that the PK/PD observations from study WA28118 in SJIA patients 1 - 17 years of age indicate that the objectives of bridging the proposed TCZ SC regimens to the approved TCZ IV regimens were achieved.

1.3. Benefit-Risk Assessment

The benefit-risk profile of SC TCZ in sJIA appears to be favorable. The efficacy and safety of SC TCZ in patients with sJIA 2 years of age and older is based on exposure and extrapolation of established efficacy and safety of IV TCZ in patients with sJIA 2 years of age and older from Study WA18221. In addition, exploratory efficacy assessments in WA28118 were consistent with improvement with treatment with SC TCZ. Further, the subcutaneous route of administration offers an alternative treatment option that may be preferable for some users. The risks of SC TCZ treatment in this patient population appear to be qualitatively similar as those seen in adults with RA treated with SC TCZ and patients with sJIA treated with IV TCZ; with the primary serious risk being an increased risk of infection. Clinicians who manage sJIA patients are familiar with TCZ safety profile.

The proposed subcutaneous dosage for sJIA patients is as follows:

- Patients < 30 kg weight - 162 mg once every two weeks
- Patients ≥ 30 kg weight - 162 mg once every week.

Study WA28118, supporting this supplemental application, was designed and conducted in keeping with the provisions of the Written Request (WR); therefore, I recommend the Study 3 of the WR, be considered fulfilled based on completion of WA28118.

Of note, the applicant proposed labeling for SC TCZ for sJIA patients (b) (4). However, the benefit-risk for sJIA patients <2 years of age has not been favorable for the TCZ IV dosing regimen, as determined during the review of BLA 125276/s115. Specifically, in Study NP25737, supporting that supplement, there were potentially increased risks of SAEs, hypersensitivity, and infections in sJIA patients <2 years of age. Further, the data from Study WA28118 are very limited to inform a different benefit-risk for the TCZ SC regiment in this age group.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Systemic JIA (sJIA) is a rare disease. • The classic presentation is quotidian fevers, arthritis, and evanescent rash alongside other systemic manifestations including the potential life-threatening complication of macrophage activation syndrome (MAS). • The peak age of onset is ages 2 to 5 years, but, by definition, it can occur anytime before the age of 16.	Systemic JIA is a serious disabling form of juvenile inflammatory arthritis with significant impact on the quality of life for patients and their families.
Current Treatment Options	• Options for therapy include NSAIDs, steroids, MTX, and biologic options for more severe manifestations. • The current treatment options include IV tocilizumab (approved), SC canakinumab (approved), SC rilonacept, and SC anakinra. • There are currently no approved drugs for treatment of sJIA in children < 2 years of age.	Treatment options are available that target specific cytokines (namely, IL-1 and IL-6). Treatment of sJIA in children <2 years of age remains an unmet medical need.
Benefit	• Study WA28118 met its primary PK endpoint with steady state Cmin in each body weight group comparable to the Cmin achieved in the corresponding body weight group upon IV administration in study WA18221. • The currently approved IV TCZ requires placement of a peripheral line every 2 weeks or, in some patients, central venous line placement. Both options can be painful and uncomfortable, and the latter can lead to an increased risk of infection. Additionally, having to receive an infusion every 2 weeks can be disruptive and inconvenient to patients and to their families. The SC formulation offers an option that may reduce inconvenience, disruption of normal activities, pain, and discomfort.	IV TCZ has already been shown to be an effective option for therapy of sJIA patients. IV therapy, however, can be disruptive in the daily lives of the patients and their families. It may also be more painful and require more invasive interventions such as central line placement. SC TCZ would avoid some of the disadvantages of IV therapy. The PK parameters at the applicant's proposed SC dosing appear to be comparable to the approved IV dosing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The basis for a regulatory action on this supplemental BLA is comparable exposure and extrapolation of established efficacy and safety of IV TCZ in patients with sJIA 2 years of age and older from Study WA18221 (the pivotal study supporting the approval of IV TCZ in this patient population, reviewed under BLA 125276). • Efficacy and safety data are supportive of the PK data. • Consistent with the known safety profile of TCZ, the safety data revealed AEs of infections, injection site reactions, and neutropenia for both body weight groups. • Two deaths occurred in the study. Both subjects were < 30 kg, and both were due to infection. One subject had sepsis; the other had pneumonia and pulmonary hemorrhage. • Three subjects were < 2 years of age in study WA28118. Although the data were consistent with the rest of the subjects in the study, conclusions are limited because of the study design and because of the small number.	The PK data established a bridge to the safety and efficacy established with the IV TCZ program in sJIA patients 2 years of age and older. The efficacy and safety data were supportive of the PK data, which did show comparability between the selected SC dosing regimens for sJIA to the approved IV TCZ doses for sJIA. The efficacy and safety were consistent in WA28118 to the IV TCZ study, WA18221. Injection site reactions were the only new AE finding, as this AE would not have been applicable to the IV presentation. Study WA28118 thus successfully supports the treatment of sJIA with SC TCZ. As the study serves as a bridge to the IV TCZ study, the indication should be the same, specifically, the treatment of sJIA in patients 2 years and older.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			Section 8.1.1 and 8.2
			X	Patient reported outcome (PRO)	Section 8.1.1 and 8.2
			X	Observer reported outcome (ObsRO)	Section 8.1.1 and 8.2
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	☐	Patient-focused drug development or other stakeholder meeting summary reports			
	☐	Observational survey studies designed to capture patient experience data			
	☐	Natural history studies			
	☐	Patient preference studies (e.g., submitted studies or scientific publications)			
	☐	Other: (Please specify)			
☐	Patient experience data that was not submitted in the application, but was considered in this review.				

X Nikolay P. Nikolov -S

Digitally signed by Nikolay P. Nikolov -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S
Date: 2018.09.12 10:16:45 -04'00'

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The ILAR 2001 classification of Juvenile Idiopathic Arthritis (JIA) defines Systemic Juvenile Idiopathic Arthritis (sJIA) as an arthritis in ≥ 1 joint for at least 6 weeks' duration in a child age < 16 years with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days and accompanied by ≥ 1 of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis.[1] It is a serious disabling form of JIA with other clinical manifestations including leukocytosis, anemia, and elevations in inflammatory markers, ferritin, and liver enzymes. Approximately 4-17% of children with JIA have sJIA.[2] Males and females are affected in equal proportions. The disease course can be monocyclic, polycyclic with relapses and period of remission, or persistent. More than half of patients have persistent disease, and these are the patients who are at greatest risk for joint damage and major growth impairment.[3,4]

Approximately 10% of children with sJIA will develop macrophage activation syndrome (MAS),[5] a life-threatening complication of sJIA that is characterized clinically by high fevers, hepatosplenomegaly, lymphadenopathy, pancytopenia, liver dysfunction, disseminated intravascular coagulation, and neurological symptoms. Laboratory features include hypofibrinogenemia, hyperferritinemia, and hypertriglyceridemia. A paradoxical decrease in erythrocyte sedimentation rate due to fibrinogen consumption can be a sign of MAS. Phagocytosis of hematopoietic cells by macrophages in the bone marrow may be seen. Reported mortality in MAS ranges from 8-22%.[6,7]

[1] Petty RE, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004; 31: 390-392.
[2] Ravelli A and Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007; 369(9563): 767-78.
[3] Singh-Grewal D., et al. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. *Arthritis Rheum*. 2006; 54: 1595-1601.
[4] Ringold S, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013; 65: 2499-2512.
[5] Ravelli A, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative. *Arthritis Rheumatol*. 2016; 68: 566-576.
[6] Minoia F, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol*. 2014; 66: 3160-3169.

Such secondary complications (e.g., growth failure, osteoporosis, deformities, and loss of function) and amyloidosis are amongst medical complications of sJIA with accompanying adverse developmental and social consequences. Systemic JIA greatly impacts the quality of life of patients and their families.

2.2. Analysis of Current Treatment Options

Intravenous tocilizumab was the first FDA-approved drug for the treatment of sJIA in 2011. Subsequently, canakinumab, a monoclonal antibody against IL-1, was approved for sJIA in 2013. Other treatments are used off-label and include the biologic therapies rilonacept and anakinra, both of which target the cytokine IL-1. Conventional disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate and leflunomide, and corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have also been used off-label for treatment of sJIA. In the 2013 update of the 2011 American College of Rheumatology (ACR) recommendations for treatment of sJIA, the initial therapy for sJIA patients with active systemic features and varying degrees of synovitis comprises of anakinra, glucocorticoid monotherapy, or NSAIDs.[8] For continued disease activity, the use of canakinumab, tocilizumab, anakinra, methotrexate, or leflunomide, TNFα inhibitor, or glucocorticoid monotherapy is recommended based on initial treatment and disease activity assessment. Table 1 includes a summary of biologic treatments for sJIA recommended in the consensus guidelines.

[7] Sawheny S, et al. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. *Arch Dis Child*. 2001; 85: 421-426.
[8] Ringold S, et al. *Arthritis Rheum*. 2013; 65: 2499-2512.

Table 1: Summary of Biologic Treatments for sJIA

Product (s) Name	Relevant Indication(s)	Year of First Approval/ Approval for sJIA	Dosing/ Administration	Efficacy Information for sJIA	Important Safety and Tolerability Issues
Tocilizumab	sJIA RA, pJIA, CRS	2010/2011	<30 kg: 12 mg/kg IV q2w ≥30 kg: 8 mg/kg IV q2w	• Improvement in ACRp30 at Week 12 and absence of fever	• Serious infections • Infusion reactions • 3% developed MAS on open label treatment • <1% with anaphylaxis
Canakinumab	sJIA Periodic fever syndromes (CAPS, TRAPS, HIDS/MKD, FMF)	2009/2013	4 mg/kg (max 300 mg) SC q4w for patients with body weight ≥ 7.5 kg	• Improvement in ACRp30 and absence of fever at Day 15 • Improvement in time to flare	• Serious infections • Injection site reactions • 5.5% developed MAS • No reports of anaphylaxis
Rilonacept	CAPS	2008/ *	Loading dose 4.4 mg/kg, up to 320 mg; then 2.2 mg/kg/week		
Anakinra	RA, NOMID	2001/ *	2-4 mg/kg/day		

* Not approved for sJIA
ACRp30 = American College of Rheumatology Pediatric 30 criteria; IV = intravenous; SC = subcutaneous; MAS = macrophage activation syndrome

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tocilizumab (TCZ) is an approved therapeutic biologic product that is available and marketed in the United States as an IV formulation (original BLA 125276, first approved January 2010) and as a SC formulation (original BLA 125472, first approved October 2013). IV TCZ is approved for treatment of moderate to severely active rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA), and cytokine release syndrome (CRS). SC TCZ is approved for moderate to severely active RA, pJIA, and giant cell arteritis (GCA). In India and Japan, IV TCZ is also approved for treatment of Castleman's disease.

3.2. Summary of Pre-submission/Submission Regulatory Activity

As noted above, BLA 125276 was approved on January 8, 2010 for IV TCZ for the treatment of adults with rheumatoid arthritis. Subsequently, BLA 125472 was approved on October 21, 2013 for SC TCZ for the treatment of adults with RA.

Intravenous TCZ was approved for sJIA with BLA 125276, Supplement 022 on April 15, 2011. As part of that approval, a Post Marketing Requirement (PMR) under the Pediatric Research Equity Act (PREA) was issued, as described below:

> *A pharmacokinetic and safety study of tocilizumab (TCZ) in patients less than 2 years old with active systemic juvenile idiopathic arthritis (sJIA)*

The original timeline required final report submission in October 2014, but this was granted a deferral extension with final report submission in November 2017. An open-label PK and safety study in patients < 2 years of age (study NP25737, N=11) was performed to fulfill this PMR. BLA 125276/Supplement 115 was approved on May 11, 2018, to include safety data (increased risk of SAEs, hypersensitivity, and infection) for patients less than 2 years of age with sJIA in the USPI Section 8.4. The supplement did not support [(b) (4)], as discussed in the review of BLA 125276/Supplement 115.

Interactions between the applicant and regulatory authorities regarding the SC presentation for sJIA began in 2012. The Committee for Medicinal Products for Human Use (CHMP) first offered scientific advice on January 19, 2012, and the FDA's advice followed shortly thereafter on February 6, 2012. The following summarizes the key interactions between the applicant and the Agency:

- The originally proposed clinical development plan for SC TCZ in sJIA included 2 studies in patients aged 2 to 17 years. The first study would be a PK/PD bridging study in 24 sJIA patients using Q10D (BW <30 kg) and QW (BW ≥30 kg) dosing regimens for 14 weeks of

treatment. This study would then be followed by a single-arm safety study of 2 years treatment duration in 70 sJIA patients to further evaluate safety of TCZ SC at the dosing regimen selected from the previous study.

- February 6, 2012, Written Response
  - In general, the Agency felt that the proposed PK/PD study was reasonable presuming a consistent exposure-response relationship is demonstrated with SC and IV in adults and children.
  - The Agency recommended enrolling more subjects into the PK/PD bridging study in order to do more dose-ranging. Also, the Agency recommended converting the open-label safety study into a LTE for the PK/PD study.
  - The Agency noted that a Q10D regimen may be difficult for patients and caregivers to follow.
  - The Agency stated that, after SC TCZ is approved for adult RA, it would be unlikely that further human factors studies would be required for pJIA or sJIA.
- The applicant subsequently amended the clinical development plan by lowering the minimum patient age to 1 year, increasing the number of patients in the PK/PD bridging study to 48 patients, and increasing the study duration to 52 weeks of treatment with a prespecified interim analysis at Week 14 in order to confirm the 2 dosing regimens selected using modeling and simulation. This PK bridging study was titled study WA28118.
- March 26, 2015, Written Response
  - The Agency agreed the SC TCZ regimen was comparable to the approved IV TCZ regimen for sJIA patients weighing ≥30 kg. The Agency also noted that the proposed SC TCZ Q2W regimen (changed from the initial Q10D regimen following the interim analysis) was reasonable to achieve a similar Cmin range with that observed with the IV regimen in sJIA patients weighing < 30 kg.
  - The Agency stated that the safety for SC TCZ in sJIA could be partially supported by the IV TCZ study in sJIA (WA18221) based on PK bridging.
- May 23, 2017, Type C Meeting Written Response
  - The Agency provided advice regarding use-related risk assessment (URRA) and human factors studies for adolescent pJIA patients who are considered suitable (by a health care provider or parent/legal guardian) for self-injection.
  - The Agency also agreed that URRA and/or human factors data for pJIA would be applicable to sJIA with appropriate justification.
- In response to the May 2017 Written Response, on July 21, 2017, the applicant submitted updates to the URRA for self-injecting pJIA and sJIA adolescent patients.
- September 28, 2017, Written Feedback of URRA and Critical tasks
  - The Agency agreed that, based on the consideration of risks associated with adolescent pJIA patients as users of TCZ pre-filled syringe (PFS) + needle safety device (NSD), no further human factors validation data were necessary.
- December 8, 2017, Pre-sBLA Preliminary Comments
  - The Agency acknowledged the safety data from study WA28118 and from the

LTE study WA29231 (through the data cut date) appeared consistent with the known safety profile for IV TCZ for pJIA, except for an increase in injection site reactions. The Agency noted that the basis for regulatory action is the PK data, and the safety and exploratory efficacy data are supportive.

- The Agency questioned whether ferritin was collected in study WA28118 as listed in the Pediatric Written Request (WR). The applicant responded shortly thereafter that ferritin was not collected. The effect of TCZ on ferritin was evaluated in the IV study (WA 18221). Also, the applicant clarified that the Pediatric Written Request stated that PD endpoints "may include" (rather than "must include) ferritin. Thus, the applicant concluded that study WA28118 fulfilled Study 3 of the WR. In response, the Agency stated that inclusion of ferritin and fulfillment of the WR would be a review issue.

Thus, in this supplement, the applicant submitted the data from study WA28118 (JIGSAW 118), a phase Ib, pharmacokinetic/pharmacodynamic (PK/PD) study to confirm SC dosing regimens in sJIA patients and to assess the safety of SC TCZ in this same population. All studies used to support this supplement are described in Section 7 of this review (Sources of Clinical Data and Review Strategy). Study WA28118 is intended to fulfill Study 3 of the WR issued to Hoffman-La Roche, Inc. on November 15, 2012, and subsequently amended on June 27, 2017. The amendment revised the timeline for submission of the reports for the studies from May 31, 2018, to September 30, 2020. Under the WR, Study 3 is a "study of PK, PD, and safety of SC TCZ in patients with sJIA 2 to 17 years of age. Efficacy of SC TCZ in sJIA patients 2 to 17 years old will be supported by the demonstrated efficacy of IV TCZ in sJIA patients 2 years of age and older that supported the approval of IV TCZ for this age group." The WR required that Study 3 enroll a sufficient number of patients to determine the SC dosing regimen that approximates the relevant PK exposure parameters of the IV sJIA dosing regimen. The WR also specified the following regarding the PK, PD, and safety endpoints. The PK endpoints must include Cmin, Cmax, Tmax, T1/2, and AUCτ at steady state. PD/efficacy parameters are considered exploratory and may include Physician Global Assessment of disease activity, Parent/patient Global Assessment of overall well-being, number of joints with limitation of movement, number of joints with active arthritis, systemic features (fever and rash), ESR, CRP, ferritin, and sIL-6R. Safety outcomes must include adverse events, tolerability, vital signs, and laboratory parameters. Immunogenicity is also to be assessed by anti-TCZ antibodies.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI inspection was not deemed necessary for this supplemental BLA. The supporting study (WA28118) was an open-label, PK-bridging study, and, thus, an OSI inspection was not conducted.

The Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation also waived the need for an inspection. See details in the Clinical Pharmacology review in Section 6.2.2.

4.2. Product Quality

No new CMC information was submitted and was not required for the regulatory decision for this supplement. The relevant information was previously reviewed in the original BLA application.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic test is submitted for review in support of this supplement.

5 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology and toxicology studies were conducted or required for the regulatory decision for this supplement. The relevant information was previously reviewed in the original BLA application.

6 Clinical Pharmacology

6.1. Summary of Clinical Pharmacology Assessment

Recommendation:
The Office of Clinical Pharmacology has reviewed the clinical pharmacology study submitted to sBLA 125472/S-031 to address the PMR and PWR requirements. This sBLA is approvable from a clinical pharmacology perspective. In addition, the clinical pharmacology information is acceptable for the fulfillment of the written request.

6.1.1. Pharmacology and Clinical Pharmacokinetics

The key clinical pharmacology findings for SC TCZ in SJIA in WA28118 that supports the extrapolation of established efficacy of IV TCZ in SJIA are summarized below:

1. After subcutaneous dosing, steady state C_{min} in study WA28118 was similar for patients in the two body weight groups, while steady-state C_{max} was higher for patients in the less than 30 kg group compared to the group at or above 30 kg (Table 2, Figure 1). The steady state C_{min} in each body weight group was comparable to the C_{min} achieved in corresponding body weight groups upon IV administration in study WA18221.

2. More than 95% of SJIA patients following TCZ SC 162 mg Q2W (<30 kg BW group) and TCZ SC 162 mg QW (≥30 kg BW group) regimens achieved a steady-state C_{min} at or above the 5th percentile of that achieved with the approved TCZ IV regimens across the spectrum of BWs in the SJIA population.

3. In subjects weighing < 30 kg, the median values of $AUC_{2weeks, ss}$ were 25% lower following 162 mg SC Q2W compared to 12 mg/kg IV Q2W regimen. For SJIA patients weighting ≥ 30 kg, the median values of $AUC_{2weeks, ss}$ were 29% lower following 162 mg SC QW compared to 8 mg/kg IV Q2W regimen. Although the median AUCs were lower compared to the IV regimen in SJIA, the steady state AUCs following SC regimens were within the range of the IV regimens in SJIA patients. Differences in AUC are not clinically relevant given the flatness of the exposure-efficacy relationship in the IV SJIA program (study WA18221); thus 30% lower AUC is unlikely to result in compromised efficacy following SC administration compared to IV regimens.

4. With the exception of slightly higher sIL-6R levels observed in the < 30 kg BW group compared with ≥ 30 kg BW group, the observed changes over time in PD biomarkers IL-6, sIL-6R, CRP and ESR were similar for both BW groups. A large variability noted in the observed IL-6 concentration data was due to 3 TCZ naive patients (BW < 30 kg) who received the 162 mg Q10D regimen (Table 7, Figure 4 - Figure 7).

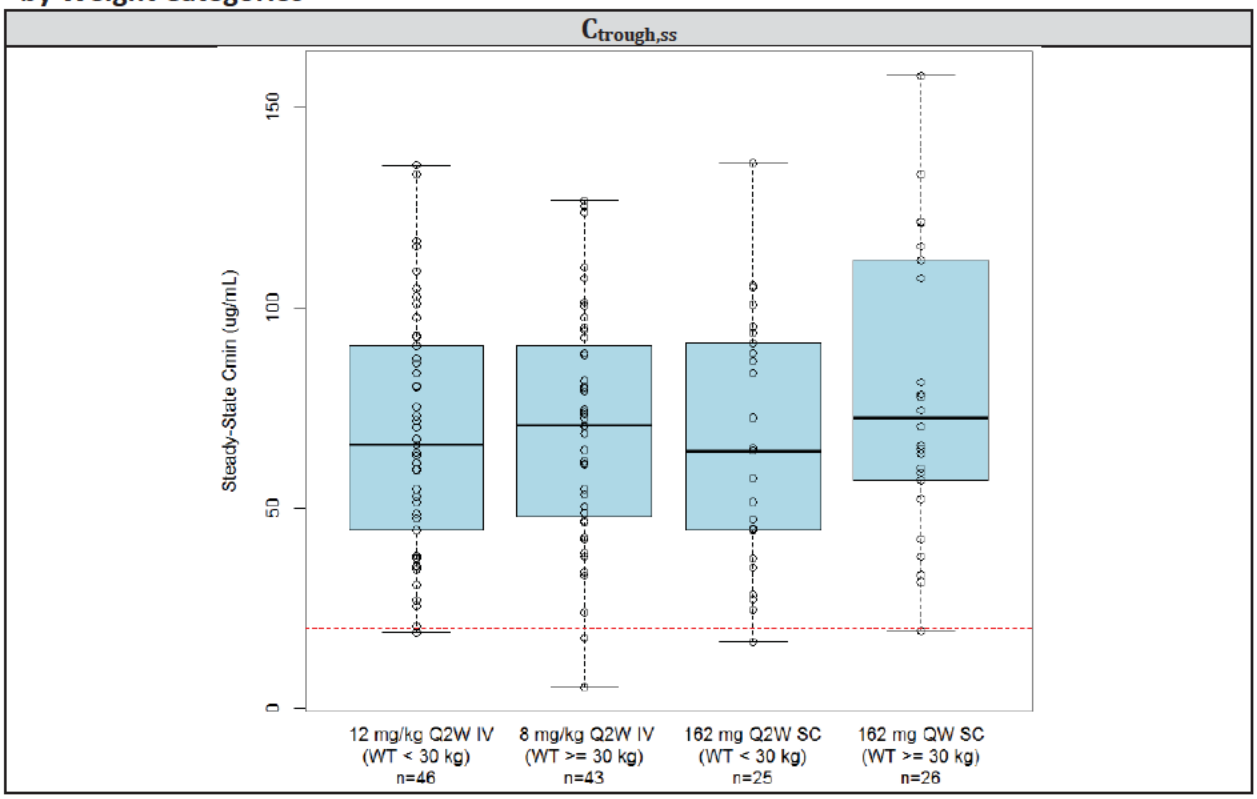
The observed tocilizumab exposure in SJIA upon subcutaneous administration supports the extrapolation of the established efficacy of intravenous ACTEMRA in SJIA patients (for details see Clinical section).

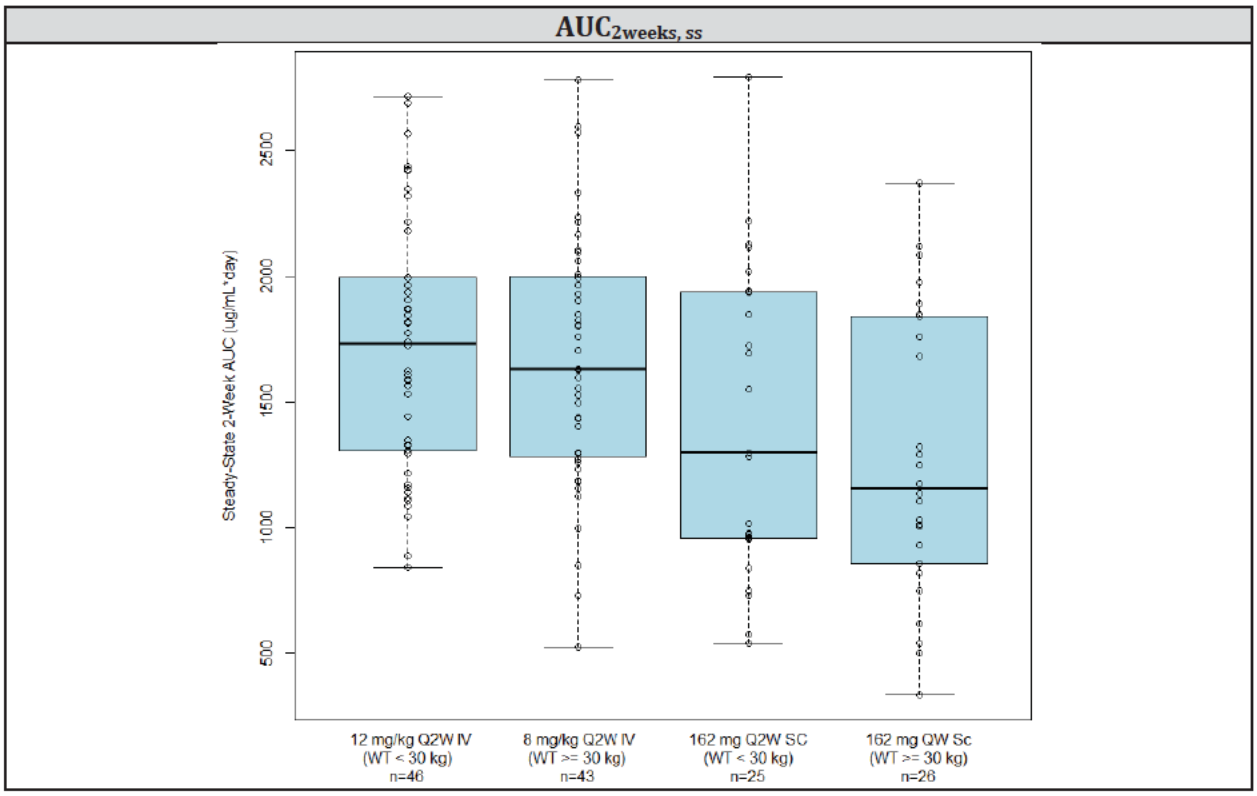
Table 2: Summary of Steady-State PK Parameter Estimates of Tocilizumab in SJIA Patients Aged 2-17 Years Old Following Subcutaneous Administration (Study WA28118) and Intravenous Administration (Study WA18221)

SJIA Subcutaneous Administration (Study WA28118)				
Dosing Regimen	**Weight Group**	**$C_{min,ss}$ (µg/mL)**	**$C_{max,ss}$ (µg/mL)**	**$AUC_{2weeks,\ ss}$ (µg·Day/mL)**
162 mg Q2W	<30 kg	64.15 (16.61 – 135.9)	126.6 (51.67 – 265.8)	1298 (539 – 2792)
162 mg QW	≥30 kg	72.37 (19.52 – 157.8)	89.8 (26.37 – 190.2)	1154 (334 – 2370)
SJIA Intravenous Administration (Study WA18221)				
Dosing Regimen	**Weight Group**	**$C_{trough,ss}$ (µg/mL)**	**$C_{max,ss}$ (µg/mL)**	**$AUC_{2weeks,\ ss}$ (µg·Day/mL)**
12 mg/kg Q2W	<30 kg	65.86 (18.99 – 135.5)	274.4 (148.8 – 444.0)	1734 (840 – 2712)
8 mg/kg Q2W	≥30 kg	70.73 (5.26 – 126.6)	253.0 (119.6 – 404.3)	1631 (526 – 2779)

(Source: CSR WA28118, Table 6, page 56)

Figure 1: Box plots of Population PK Model Predicted Steady-State Trough Concentration Values (top) and AUC Values (bottom) for SJIA patients following IV and SC Dosing Regimens by Weight Categories





(Source: Population PK and PK-PD Analyses Report 1084039, Figures 49-50, pp 114-115)

6.1.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended intravenous dosage for SJIA patients is as follows:
Patients < 30 kg weight - 12 mg per kg every 2 weeks
Patients ≥ 30 kg weight - 8 mg per kg every 2 weeks

The proposed subcutaneous dosage for SJIA patients is as follows:
Patients < 30 kg weight - 162 mg once every two weeks
Patients ≥ 30 kg weight - 162 mg once every week

Therapeutic Individualization

Not Applicable.

Outstanding Issues

None.

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. General Pharmacology and Pharmacokinetic Characteristics

Tocilizumab (RO4877533, TCZ) is a humanized anti-human IL-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass produced using recombinant DNA technology. The subcutaneous formulation of tocilizumab (BLA 125472) was originally approved on October, 2013 for treatment of moderate to severely active RA in adults with an inadequate response to one or more disease modifying anti-rheumatic drugs. Tocilizumab intravenous formulation (BLA 1125276, approved in January, 2010) is indicated for the treatment of adult RA, and for patients 2 years of age and older with polyarticular Juvenile Idiopathic Arthritis (PJIA) or systemic Juvenile Idiopathic Arthritis (sJIA).

Mechanism of action
Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6Rα and mIL-6Rα), and inhibits IL-6 mediated signaling.

Chemistry and physicochemical properties

Tocilizumab molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulfide linkages. The molecular formula is $C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$ (polypeptide moiety only). The molecular weight is approximately 149 kDa (b) (4) .

6.2.2. Clinical Pharmacology Questions

What was the criteria set in the Pediatric Written Request, and were the criteria fulfilled in the Study?

The Clinical Pharmacology related criteria set out in the PWR for SC TCZ in SJIA patients ages 2 – 17, and the Sponsor's obligation to fulfil the criteria are summarized in Table 3.

Table 3: Clinical Pharmacology Criteria Set Out in the Pediatric Written Request

Written Request	***Were Clinical Pharmacology related criteria fulfilled***
Study 3: **A study of the pharmacokinetics, pharmacodynamics, and safety of SC TCZ in patients with SJIA 2 to 17 years of age.** Efficacy of SC TCZ in SJIA patients 2 to 17 years old will be supported by the demonstrated efficacy of IV TCZ in SJIA patients 2 years of age and older that supported the approval of IV TCZ for this age group.	***Yes***
Objectives: The primary objective of this study is to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of TCZ in patients with SJIA following SC administration for 14 weeks. Specifically, the aim will be to achieve a similar C_{min} range with the SC route of administration to that observed with the IV route of administration in the study that served as the basis for approval of IV TCZ in SJIA. The exploratory objective is to evaluate efficacy of TCZ in combination with stable ongoing therapy in patients with SJIA following SC administration for 14 weeks.	***Yes***
Patients to be studied: *Age group in which studies will be performed*: • SJIA patients 2 to 17 years of age *Number of patients to be studied:* Study 3, SC PK-PD Bridging Study in SJIA: Enroll sufficient numbers of patients to determine the SC dosing regimen that approximates the relevant PK exposure	 ***Yes*** ***Yes, 44 subjects completed the study***

Written Request	***Were Clinical Pharmacology related criteria fulfilled***
parameters of the IV SJIA dose regimen. <u>*Representation of Ethnic and Racial Minorities:*</u> The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.	***Most patients were Caucasians (80.4%), and of non-Hispanic ethnicity (76.5%)***
Study endpoints: • *Pharmacokinetic Endpoints:* The pharmacokinetic endpoints for SC PK-PD bridging study in SJIA patients must include C_{min}, C_{max}, T_{max}, $T_{1/2}$ and AUC_{τ} at steady state. • *Pharmacodynamic/Efficacy Endpoints:* Pharmacodynamic (PD)/efficacy parameters will be regarded as exploratory and may include Physician Global Assessment of disease activity, Parent/patient Global Assessment of overall well-being, Number of joints with limitation of movement, Number of joints with active arthritis, Systemic features (fever and rash), ESR, CRP, ferritin and sIL-6R.	***Yes*** ***Yes***
Statistical information, including power of studies and statistical assessments: SC PK-PD Bridging Study in SJIA: A pediatric PK study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power in the age group to be studied. The proposed sample size must be based on the above criterion utilizing inter-subject PK variability from Study WA18221. In order to calculate the sample size, the method under "Sample Size Calculation for Rich PK Sampling Design Intended for NCA Analysis" in the paper by Wang Y et al. (Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol published online December 12, 2011) should be followed. An alternative method to compute the 95% CI without involving the empirical Bayesian estimate is also described in the cited paper (under "Sample Size Calculation for Sparse/Rich PK Sampling Design Intended for popPK Analysis").	***Based on the methodology proposed in Wang et al. (2012) on determining sample size for pediatric PK studies, an initial sample size of approximately 48 patients would allow targeting a probability (power) of at least 80% to have the 95% confidence interval (CI) within 60% and 140% of the population mean estimates for the PK parameters in the age group to be studied.*** ***Yes***

What was the dose justification used for Study WA28118?

Exposure−response analyses using data from a previously conducted SJIA IV study WA18221 demonstrated relationships between TCZ C_{min} at steady state and the probability of achieving JIA ACR30, ACR50, and ACR70 responses. TCZ C_{min} level at steady state has been shown to be an adequate marker of the extent and duration of saturation of IL-6R. The effect of TCZ is correlated with the extent and duration of the saturation of the IL-6R. Bridging between the IV and SC TCZ formulations is based on achieving similar TCZ C_{min} following subcutaneous administration as was observed following IV administration.

PK simulations were conducted with established population PK model of TCZ based on pediatric IV data from Study WA18221 and adult SC data from Studies WA22762 and NA25220. Based on the initial PK simulation, a 162-mg QW dose in patients with SJIA weighing ≥ 30 kg was estimated to provide a mean ± SD C_{min} of 58 ±20 µg/mL, which is comparable to the mean ±SD C_{min} (58 ±23 µg/mL) of all patients in the IV Study WA18221. Therefore, this dose was selected for testing in patients weighing ≥ 30 kg in Study WA28118. In patients weighing < 30 kg, a dose of 162 mg Q2W resulted in a mean ±SD C_{min} of 29 ±13 µg/mL, which was lower than that observed in Study WA18221; while a dose of 162 mg QW resulted in a mean ±SD C_{min} of 100 ±35 µg/mL, which was substantially higher than that previously observed in Study WA18221. In patients weighing < 30 kg, a dose of 162 mg of SC TCZ Q10D was selected since this dose was predicted to provide a C_{min} of 58 ±22 µg/mL in patients weighing as low as 10 kg, which was comparable to the C_{min} observed in Study WA18221.

Following review of the data from the planned interim analysis of the first 28 patients (8 patients < 30 kg and 20 patients ≥ 30 kg) who completed Week 14 of the study, the recommended dosing regimen for patients with body weight < 30 kg was changed from 162 mg Q10D to 162 mg Q2W. The dosing regimen for the ≥ 30 kg patients remained unchanged at 162 mg QW. Based on the interim results, the revised Q2W dosing regimen in patients < 30 kg was predicted to achieve a range of C_{min} closer to that observed by the approved IV TCZ therapy in this weight group (Study WA18221) while in the ≥ 30 kg a good match of C_{min} was already achieved.

What is the composition of to-be-marketed formulation of tocilizumab?

Tocilizumab SC is supplied as a sterile, colorless to slightly yellowish, preservative-free liquid solution in a single-use 1 mL prefilled syringe (PFS) for subcutaneous (SC) injection, delivering 162 mg tocilizumab/0.9 mL. Table 4 lists the qualitative and quantitative composition of the Drug Product.

Table 4: Qualitative and Quantitative Composition of Tocilizumab SC PFS Formulation (162 mg/0.9 mL)

Composition of Actemra SC PFS 162 mg/0.9 mL

Ingredient	Nominal Amount/PFS	Concentration	Function	Specifications
Tocilizumab	162 mg	180 mg/mL	Active ingredient	In-house specifications (Section S.4.1 Specification, Drug Substance)
Polysorbate 80			(b) (4)	
L-Arginine				
L-Arginine Hydrochloride				
L-Methionine				
L-Histidine				
L-Histidine Hydrochloride Monohydrate				
Total Volume Adjusted with Water for Injection				

NA=not applicable; QS=quantity sufficient.
[a] pH approximately 6.0.

(Source: Module 3.2.P.1, Description and Composition of the Drug Product, Table P.1-1, page 1)

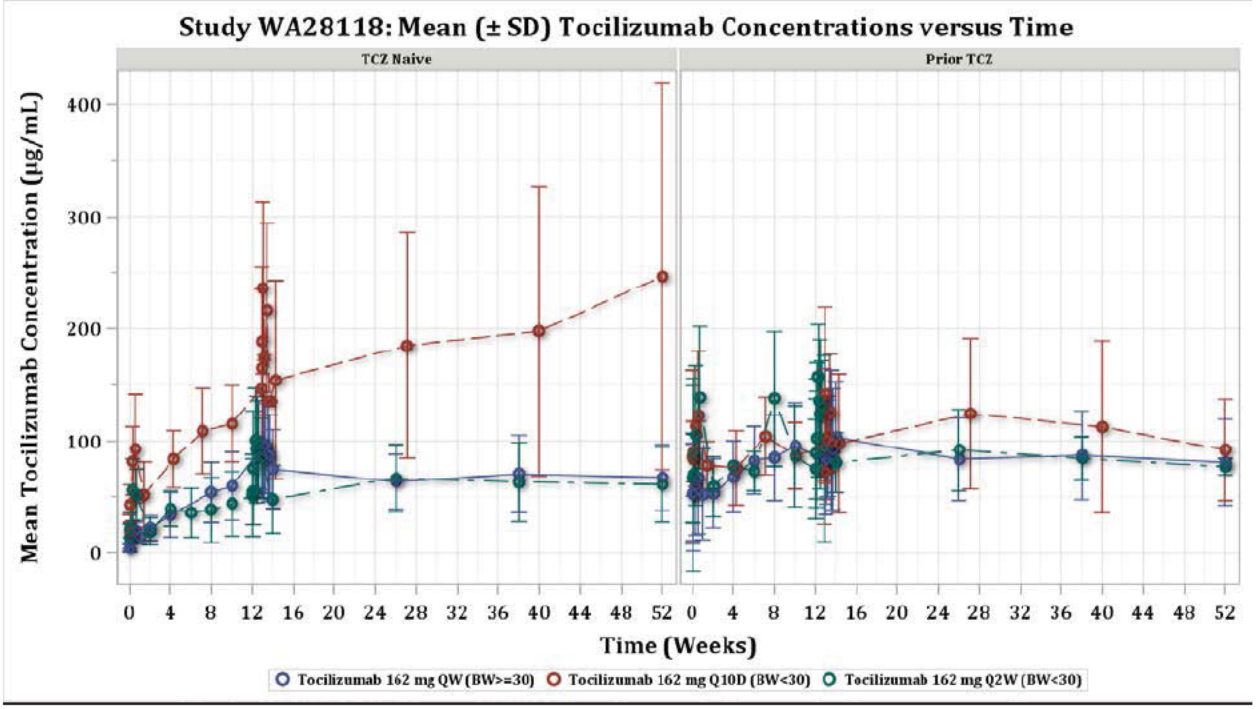
What are the findings from OSIS inspection?

The Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation declined to conduct the inspection of the analytical site. The rationale for this decision was that OSIS recently inspected the site, and although the last inspection was classified as a Voluntary Action Indicated (VAI), based on the inspectional outcome and OSIS's recommendation to the review division, an inspection is not needed at this time. See memo dated 06 Jul 2018 from Shila S Nkah in DARRTS, Reference ID 4291732. A previous request to OSIS for inspection (BLA 125472/S-028) of the same bioanalytical site was also declined and OSIS had at that time recommended accepting the bioanalytical data (for Study WA28117) because OSIS had recently inspected the site.

What were the pharmacokinetics of tocilizumab following subcutaneous administration to SJIA patients aged 2 – 17 years?

Representative mean serum TCZ concentration-time profiles for SJIA patients during the 52-week treatment are illustrated in Figure 2 below. Observed pre-dose concentrations reached a stable level around Week 14 following TCZ administration for both TCZ naive and prior TCZ patients for both 162 mg Q2W (BW < 30 kg) and QW (BW ≥ 30 kg) regimens.

Figure 2: Mean(±SD) TCZ Concentrations from Study WA28118



The observed and population PK model-computed steady-state PK parameters $C_{min,ss}$, $C_{max,ss}$, and $AUC_{2weeks,ss}$ in sJIA patients following 162 mg SC Q2W (< 30 kg) from Study WA28118 are shown in Table 5. Similarly, the observed and population PK model computed steady-state PK parameters $C_{min,ss}$, $C_{max,ss}$, and $AUC_{2weeks,ss}$ in SJIA patients following 162 mg SC QW (≥ 30 kg) from Study WA28118 are shown in Table 6 . The pop PK model predicted the parameters reasonably well.

Table 5: Summary of Week 12 Observed Steady-State PK Parameters for TCZ for SJIA Patients < 30 kg following 162 mg SC Q2W Regimen

	$C_{min,ss}$	$C_{max,ss}$	$AUC_{2weeks,ss}$
Observed[a,b]	77.8 (9.23 – 369)	152 (41.6 – 369)	917 (15.8 – 4100)
Model-Computed[c,d]	64.15 (16.61 – 135.9)	126.6 (51.67 – 265.8)	1298 (539 – 2792)

[a]Median (range) is reported reported for all PK parameters
[b]n = 25 for all parameters
[c]Median (range) is reported reported for all PK parameters
[d]n = 26 for all parameters

(Source: Reviewer analysis for observed parameters, and CSR WA28118, Table 6, page 56 for model computed parameters)

Table 6: Summary of Week 12 Observed Steady-State PK Parameters for TCZ for SJIA Patients ≥ 30 kg following 162 mg SC QW Regimen

	$C_{min,ss}$	$C_{max,ss}$	$AUC_{2weeks,ss}$
Observed[a,b]	74.0 (1.12 – 155)	94 (44.9 – 253)	953 (9.92 – 2327)
Model-Computed[c,d]	72.37 (19.52 – 157.8)	89.8 (26.37 – 190.2)	1154 (334 – 2370)

[a]Median (range) is reported reported for all PK parameters
[b]n = 25 for all parameters
[c]Median (range) is reported reported for all PK parameters
[d]n = 26 for all parameters

(Source: Reviewer analysis for observed parameters, and CSR WA28118, Table 6, page 56 for model computed parameters)

What were the findings of the Population PK analysis?

The main objectives of the population PK analysis were to:

(a) establish a predictive population model that describes pharmacokinetics of tocilizumab following intravenous and subcutaneous administration to patients with SJIA.
(b) estimate population parameters of the model, including inter-individual variability of model parameters and intra-individual variability of the tocilizumab concentrations in patient population.
(c) identify covariate factors that may influence SC absorption, disposition, and elimination of tocilizumab in patients with SJIA.
(d) determine post-hoc estimates for derived PK parameters (steady-state AUC, C_{max} and C_{trough}) for patients of study WA28118

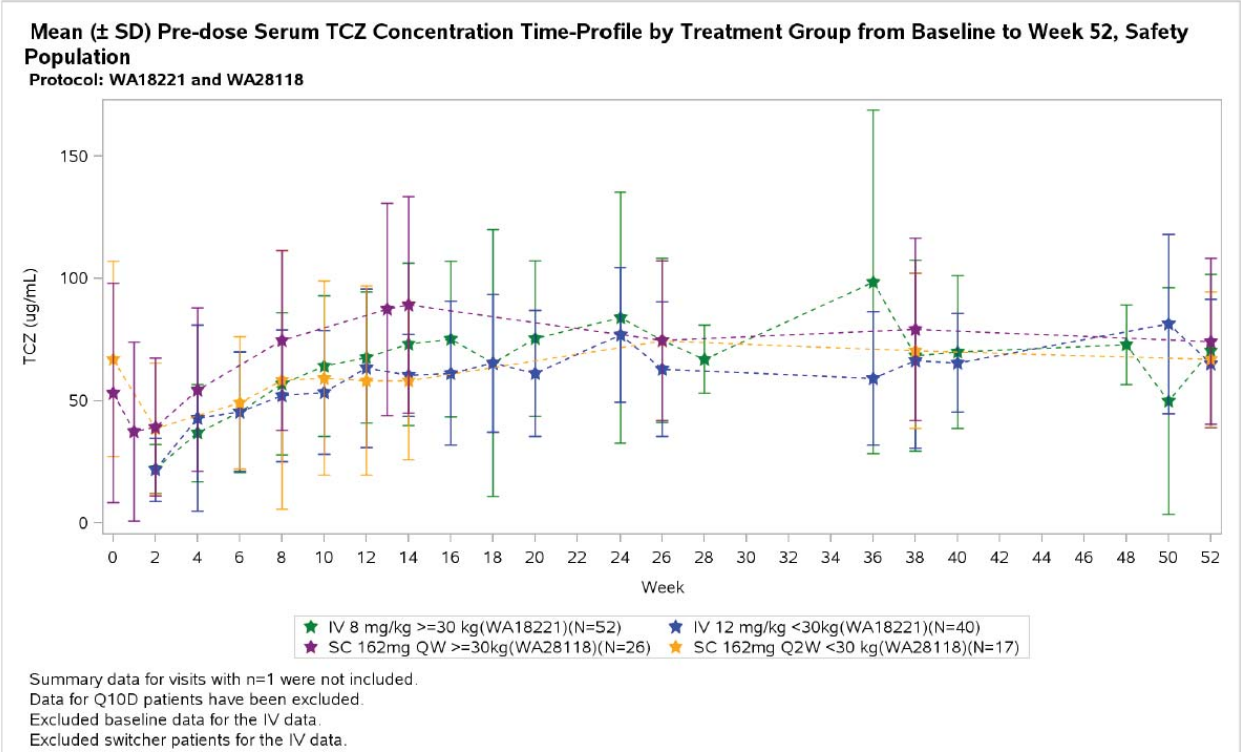
An established model for SJIA patients based on pediatric TCZ IV data from Study WA18221 and adult TC SC data from Studies WA22762 and NA25220 was used without modifications as a starting point for the model building process. The final model was a two-compartment model with the first-order absorption (following SC administration) and parallel linear and Michaelis-Menten elimination. Consistent with prior knowledge of TCZ IV in SJIA patients, body weight was the most significant covariate contributing to the variability in the PK parameters. Tocilizumab PK parameters increased with increasing body size (BSA and height). Additionally, SC absorption parameters (absolute bioavailability and absorption rate constant) decreased with increasing BMI. Based on model diagnostics, the final population PK model appears to reasonably predict the PK profiles following IV and SC administration in patients with SJIA.

Based on the population PK model predicted concentration - time profiles for exposure comparison (Table 2), and observed pre-dose concentration time profile (Figure 3):

- $C_{max,ss}$ values were lower following SC administration, compared to IV for both weight groups

- $C_{min, ss}$ values following SC and IV administrations were comparable for both weight groups.
- For SJIA patients weighing < 30 kg, the median values of $AUC_{2weeks, ss}$ were 25% lower following 162 mg SC Q2W compared to 12 mg/kg IV Q2W regimen. For SJIA patients weighting ≥ 30 kg, the mean values of $AUC_{2weeks, ss}$ were 29% lower following 162 mg SC QW compared to 8 mg/kg IV Q2W regimen.

Figure 3: Mean Pre-dose Serum Tocilizumab Concentration-Time Profiles from Baseline to Week 52 by Treatment Group



(Source: 18Jun2018 Response to Information Request, Figure, page 6)

Further details are listed in the pharmacometric report in Section 12.3.

Is the proposed dosing regimen appropriate based on the exposures observed in Study WA28118?

1. After subcutaneous dosing, steady state C_{min} was similar for patients in the two body weight groups, while steady-state C_{max} was higher for patients in the less than 30 kg group compared to the group at or above 30 kg (Table 2).

2. At steady state, the median C_{min} achieved with TCZ SC was similar for patients in both BW groups, and the range of C_{min} largely overlapped for both BW groups. More than

95% of SJIA patients following TCZ SC 162 mg Q2W (<30 kg BW group) and TCZ SC 162 mg QW (≥30 kg BW group) regimens achieved a steady-state C_{min} at or above the 5th percentile of that achieved with the approved TCZ IV regimens across the spectrum of BWs in the SJIA population.

3. In subjects weighing < 30 kg, the median values of $AUC_{2weeks, ss}$ were 25% lower following 162 mg SC Q2W compared to 12 mg/kg IV Q2W regimen. For SJIA patients weighting ≥ 30 kg, the mean values of $AUC_{2weeks, ss}$ were 29% lower following 162 mg SC QW compared to 8 mg/kg IV Q2W regimen. Although the median AUCs were lower compared to the IV regimen in SJIA, the steady state AUCs following SC regimens were within the range of the IV regimens in SJIA patients. Difference in AUC are not clinically relevant given the flatness of the exposure-efficacy relationship in the IV SJIA program (study WA18221), thus 30% lower AUC is unlikely to result in compromised efficacy following SC administration compared to IV regimens.

4. Except for IL-6 values, the median sIL-6R, CRP and ESR values were similar between SC and IV administrations. A large variability noted in the observed IL-6 concentration data was due to 3 TCZ naive patients (BW < 30 kg) who received the 162 mg Q10D regimen.

PK/PD observations from study WA28118 in SJIA patients 1 - 17 years of age indicate that the objective of bridging the proposed TCZ SC regimens to the approved TCZ IV regimens were achieved.

What were the pharmacodynamics of tocilizumab following subcutaneous administration to SJIA patients aged 2 – 17 years?

A comparison of PD endpoints, IL-6, sIL-6R, CRP and ESR between SC and IV administrations of tocilizumab in PJIA patients is shown in Table 7. With the exception of slightly higher sIL-6R levels observed in the < 30 kg BW group compared with ≥ 30 kg BW group, the observed changes over time in PD biomarkers IL-6, sIL-6R, CRP and ESR were similar for both BW groups. A large variability was noted in the observed IL-6 concentration data was due to 3 TCZ naive patients (BW < 30 kg) who received the 162 mg Q10D regimen.

Table 7: Comparison of Mean and Median Steady-State PD Markers (PK Population)

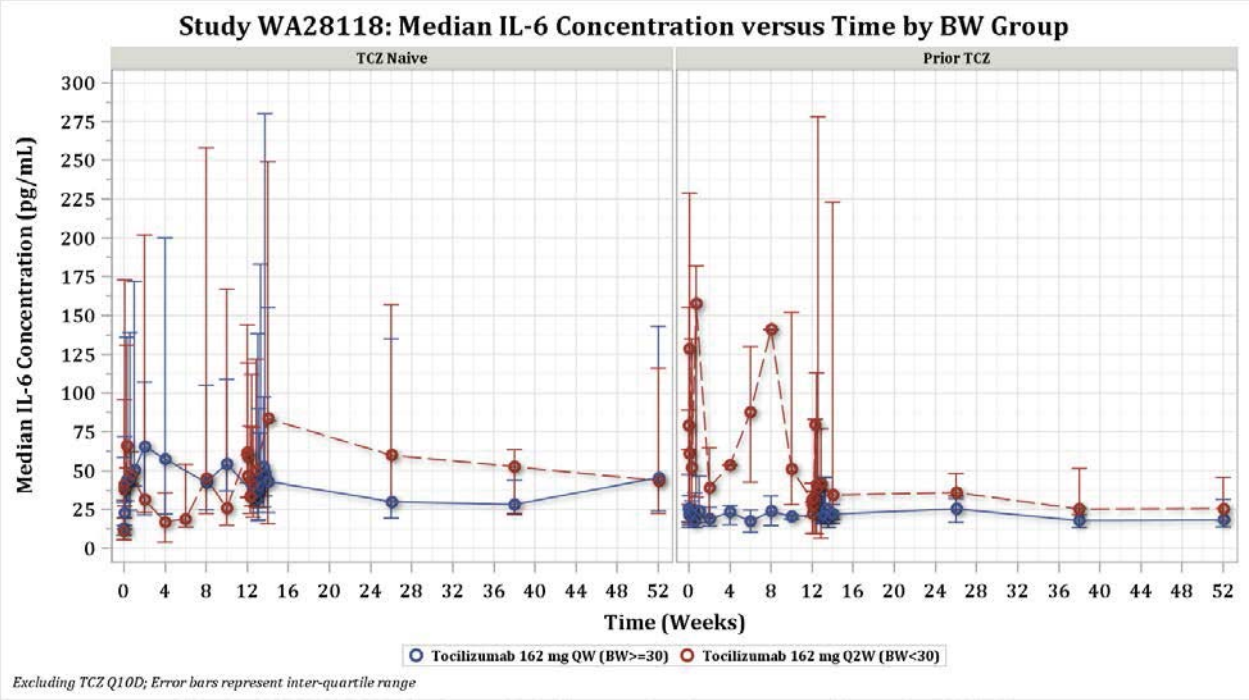
Dosing Regimen	n	Visit	Mean ± SD	Median (min – max)
C-Reactive Protein (mg/dL)				
TCZ SC in SJIA				
162 mg Q10D or Q2W (BW < 30 kg)	25	Week 52	0.273 ± 0.249	0.200 (0.20 – 1.23)
162 mg QW (BW ≥ 30 kg)	26	Week 52	0.381 ± 0.549	0.200 (0.20 – 2.45)
TCZ IV in SJIA				
8 mg/kg (BW ≥ 30 kg)	35	Week 12	0.061 ± 0.114	0.025 (0.012 – 0.658)
12 mg/kg (BW < 30 kg)	37	Week 12	0.376 ± 2.081	0.013 (0.010 – 12.688)
Erythrocyte Sedimentation Rate (mm/h)				
TCZ SC in SJIA				
162 mg Q10D or Q2W (BW < 30 kg)	19	Week 52	2.11 ± 1.56	2.00 (0.0 – 5.0)
162 mg QW (BW ≥ 30 kg)	23	Week 52	3.65 ± 4.59	2.00 (1.0 – 24.0)
TCZ IV in SJIA				
8 mg/kg (BW ≥ 30 kg)	36	Week 12	4.0 ± 4.1	3.0 (0.0 – 21.0)
12 mg/kg (BW < 30 kg)	37	Week 12	3.0 ± 12.1	2.0 (0.0 – 8.0)
Interleukin-6 (pg/mL)				
TCZ SC in SJIA				
162 mg Q10D or Q2W (BW < 30 kg)	17	Week 52	60.429 ± 68.889	40.800 (13.70 – 297.00)
162 mg QW (BW ≥ 30 kg)	20	Week 52	49.947 ± 55.439	25.20 (8.43 – 182.00)
TCZ IV in SJIA				
8 mg/kg (BW ≥ 30 kg)	35	Week 12	281.02 ± 360.158	100.00 (22.90 – 1370.00)
12 mg/kg (BW < 30 kg)	28	Week 12	144.57 ± 236.424	73.10 (18.60 – 1210.00)
Soluble IL-6 Receptor (ng/mL)				
TCZ SC in SJIA				
162 mg Q10D or Q2W (BW < 30 kg)	18	Week 52	764.83 ± 271.32	737.0 (270.0 – 1490.0)
162 mg QW (BW ≥ 30 kg)	20	Week 52	558.90 ± 227.28	598.0 (199.0 – 1070.0)
TCZ IV in SJIA				
8 mg/kg (BW ≥ 30 kg)	35	Week 12	772 ± 179.6	776 (426 – 1140)
12 mg/kg (BW < 30 kg)	33	Week 12	770 ± 204.6	790 (53 – 1040)

(Source: CSR for report WA28118, pages 273, 279, 283, 287; CSR for report WA18221, pages 530, 532, 687, 689)

IL-6

Median serum IL-6 concentration increased rapidly 1 week after the first dose and fluctuated slightly between doses after the first dose through Week 12 for both the 162 mg Q2W (BW < 30 kg) and 162 mg QW (BW ≥ 30 kg) regimens for the TCZ naive patients (Figure 4). Prior TCZ patients for both the 162 mg Q3W (BW < 30 kg) and 162 mg Q2W (BW ≥ 30 kg) regimens showed a similar trend for the median serum IL-6 concentration-time profiles. Median serum IL-6 concentrations from Week 14 through Week 52 were similar for both the 162 mg Q2W (BW < 30 kg) and 162 mg QW (BW ≥ 30 kg) regimens and TCZ status (TCZ naive and prior TCZ).

Figure 4: Median Serum IL-6 Concentrations in TCZ Naïve and Previously Exposed to TCZ SJIA Patients 2 - 17 years of Age

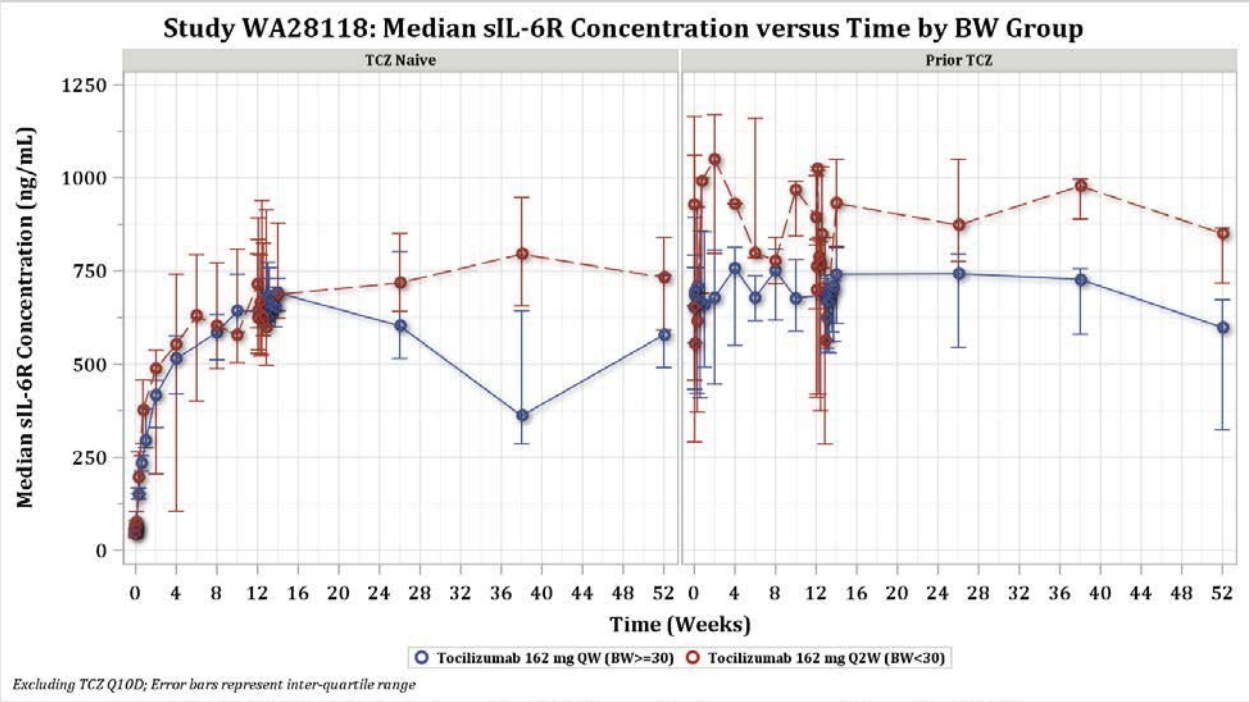


sIL-6R

Median sIL-6R concentration increased after the first dose for both the 162 mg Q2W (BW < 30 kg) and 162 mg QW (BW ≥ 30 kg) regimens through Week 12 for the TCZ naive patients and remained relatively stable through Week 52. Median sIL-6R concentration remained relatively stable from the first dose up to Week 52 for the patients previously exposed to TCZ, except at Week 52 for the prior TCZ patients weighing ≥ 30 kg. Due to the small patient number (n = 5) and an unusually low sIL- 6R concentration at this time point observed in 2 patients, the observed median sIL-6R concentration was low.

Slightly higher changes in sIL-6R concentration were observed for patients treated with 162 mg Q2W (BW < 30 kg) compared to patients treated with 162 mg QW (BW ≥ 30 kg) regimen for both TCZ naive and patients previously exposed to TCZ (Figure 5).

Figure 5: Median Serum sIL-6R Concentrations in TCZ Naïve and Previously Exposed to TCZ SJIA Patients 2 – 17 years of Age



C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR)

The levels of PD markers of inflammation, CRP and ESR, showed a rapid decline after inititation of treatment and remained low from Week 4 through Week 52 for TCZ naïve patients. For patients with prior exposure to TCZ, the median CRP and ESR concentration levels remained low from first dose up to Week 52. (Figure 6 and Figure 7, respectively). Comparable changes in CRP and ESR from Week 4 through Week 52 for the 162 mg Q3W (BW < 30 kg) and 162 mg Q2W (BW ≥ 30 kg) regimen were observed for both TCZ naive and patients with prior exposure to TCZ.

Figure 6: Median C-Reactive Protein Concentrations Following Tocilizumab 162 mg Q2W or 162 mg Q3W in TCZ Naïve Patients and Patients with Prior Exposure to TCZ

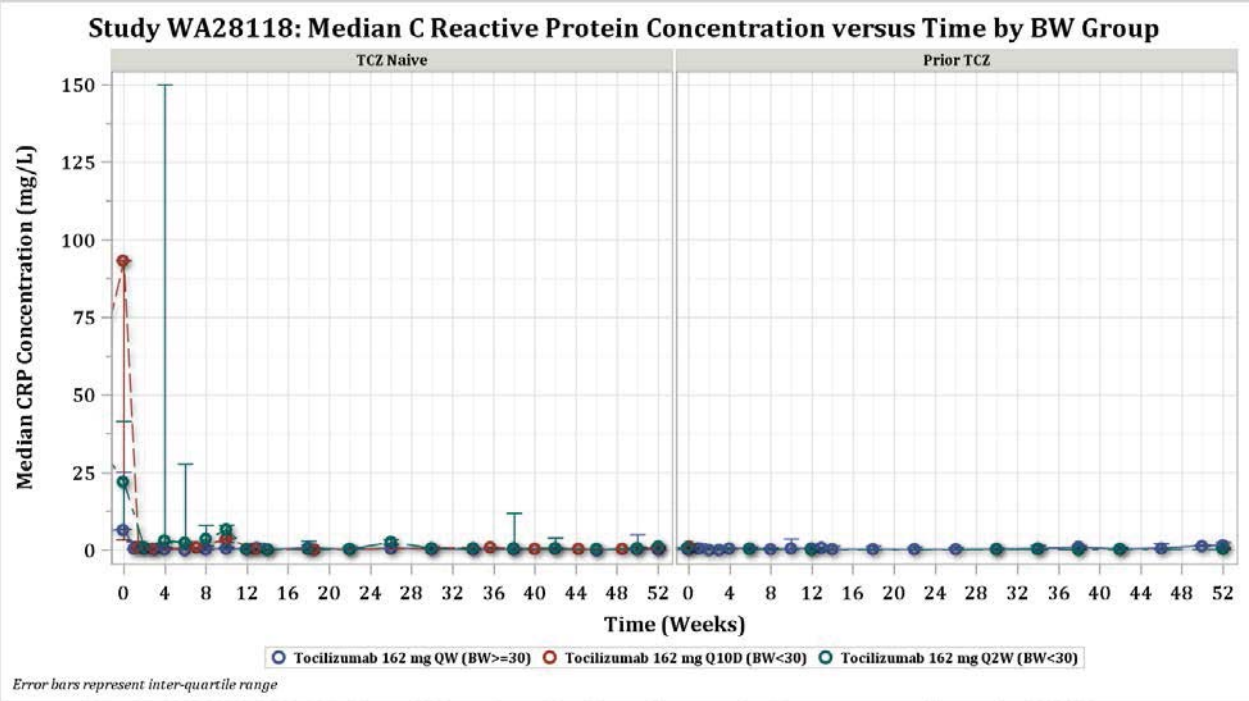
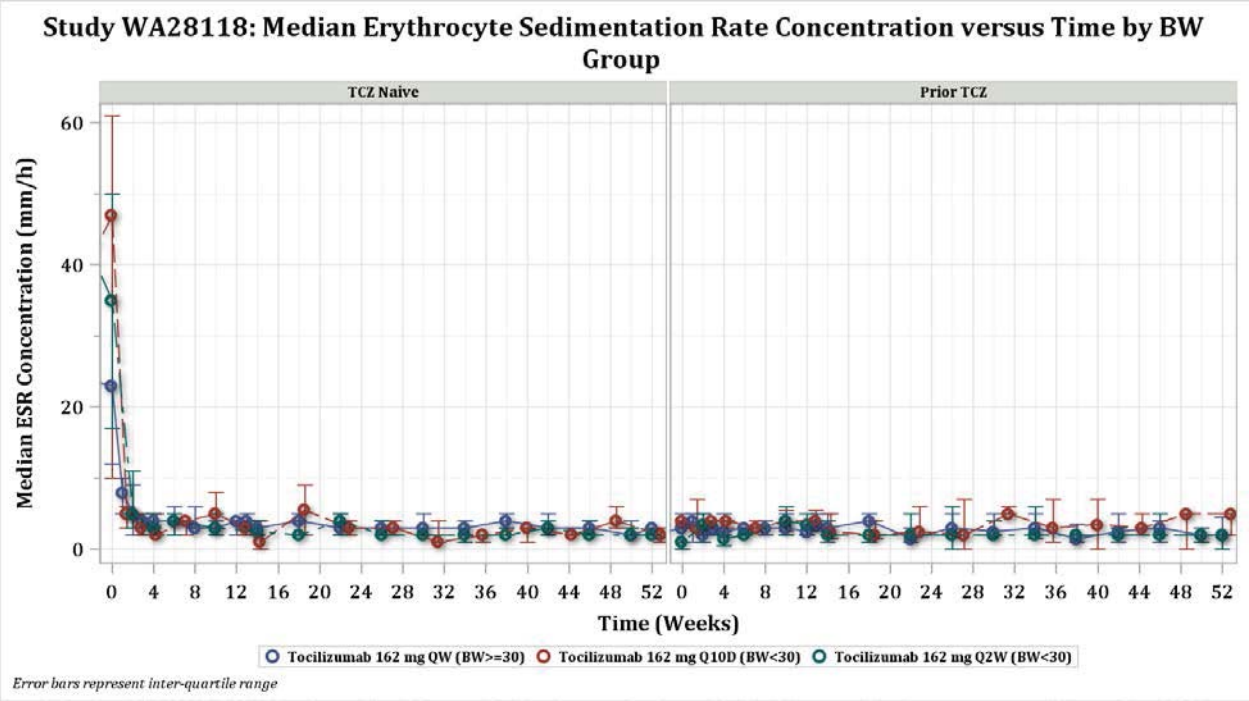


Figure 7: Median ESR Following Tocilizumab 162 mg Q2W or 162 mg Q3W in TCZ Naïve Patients and Patients with Prior Exposure to TCZ



What were the Immunogenicity findings?

Immunogenicity was assessed by taking samples for anti-drug antibody (ADA) at baseline prior to TCZ infusion, at approximately 3-month intervals during the study, and at the last study visit or at the time of early withdrawal from the study.

Results of baseline screening assay were available for all 51 patients, with 46 patients (90.2%) having at least one post-baseline screening assay result qualifying them as evaluable patients. Though 3 patients (5.9%), of which 1 patient had prior TCZ experience, tested screening assay positive at baseline, none were ADA positive in the confirmation assay. These 3 patients had a negative confirmation assay post-baseline. All patients were ADA negative post-baseline.

Does the clinical pharmacology program provide supportive evidence of effectiveness?

See section 6.2.1.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Refer to previous section.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Not applicable.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable.

Question on clinically relevant specifications (TBD)?

Not applicable.

Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?

a. **Tocilizumab:**

Concentrations of tocilizumab in human serum samples were determined using a validated enzyme-linked immunosorbent assays (ELISA). Briefly, TCZ is captured with biotin-labeled interleukin soluble receptor (IL-6sR) in streptavidin coated microtiter plates in the first step. The bound TCZ can be detected by digoxigenylated anti-TCZ antibodies followed by an anti-DIG-POD (poly) conjugate and ABTS as a substrate. The quantity of bound peroxidase is determined through a chromogenic reaction with the ABTS substrate and photometric detection (wavelength at 405 nm and 490 nm as reference). The absorbance is proportional to the TCZ concentration in the sample.

Calibration was performed using the Four Parameter logistic model with a weighting factor of 1, over an analytical assay range of 1.25 ng/mL to 160 ng/mL tocilizumab in 40-fold diluted serum equivalent to 50 ng/mL to 6400 ng/mL in neat serum). The assay sensitivity in terms of LLOQ (lower limit of quantitation) and ULOQ (upper limit of quantitation) were 100 ng/mL, and 3200 ng/mL, respectively, for TCZ (concentration in neat serum).

The precision and accuracy of the assay, as determined from the analysis of quality control samples ranged from 9.8% to 10.7% (precision) and from 93.2% to 101.1% (accuracy). The analytical PK assay met the regulatory criterion for acceptable performance during sample analysis. The intra- and inter-run accuracy and precision of at least 67% of all quality controls were within ± 20% of their nominal concentrations and at least 50% of quality controls at each

concentration were within ± 20% of their nominal values. The study samples were stored and analyzed within the validated conditions.

The summary of the acceptance criteria for the bioanalytical validation methods of tocilizumab, used in the PK study WA28118 included in this application are summarized in Table 8.

Table 8: Bioanalytical Method Validation for Tocilizumab

Tocilizumab	
Minimum required dilution	40-fold
Sensitivity of assay	100 ng/mL
Precision (CV)	10.0% to 89.8% (9.7% to 10.2%)*
Accuracy	97.7% to 116.5% (97.7% to 104.4%)*

(Source: CSR for Study WA28118, synopsis of the bioanalytical reports for tocilizumab, page 2668)

b. Anti-tocilizumab antibodies

Anti-tocilizumab (TCZ) antibodies were determined in human serum using a validated enzyme-linked immunosorbent assay (ELISA) method. Immunogenicity testing of samples was done in a tiered approach. Briefly, in the Screening assay (tier 1), biotin-labeled-Tocilizumab (TCZBi) was bound to a streptavidin-coated microtiter plate in the first step. The samples were pre-incubated for 1 h with a fixed quantity of digoxigenylated TCZ (TCZ-DIG) in a separate non-binding microtiter plate (pre-incubation plate), allowing the anti- Tocilizumab antibodies in the samples to bind to TCZ-DIG. After this step the samples were transferred into a streptavidin coated microtiter plate containing bound biotinylated TCZ. The anti-TCZ antibody/TCZ-DIG complexes of the pre-incubated solution bound to the immobilized TCZ-Bi. The bound TCZBi/ anti-TCZ antibody/TCZ-DIG complex was detected with peroxidase-labeled anti-DIG antibodies. The amount of bound peroxidase was determined with ABTS substrate. The absorbance (A405-A490 value) was proportional to the amount of anti-TCZ antibodies present in the sample. Serum samples found positive in the Screening assay, the presence of specific anti-TCZ antibodies was confirmed or excluded using the same ELISA method with an appropriate immunocompetition step (addition of excess TCZ, confirmatory assay, tier 2). The assay was conducted using 150 µL of 10-fold diluted human serum. The calibration range in assay concentrations was 0.781 to 100 ng-eq/mL mL, with an assay sensitivity of 7.18 ng-eq./ml in native serum. Precision ranged from 7.3% to 7.8% (Screening assay) and 0.0% to 5.8% (Confirmatory assay) and accuracy ranged from 96.5% to 98.3% (Screening assay) and 100.0% to 107.9% (Confirmatory assay).

For details on the bioanalytical validation methods of anti-tocilizumab antibodies, used in the PK study WA28118 included in this application, and Neutralizing anti-TCZ antibodies

determined in human serum using a validated ELISA method, refer to OBP review for further information.

OCP Conclusions and Recommendations:

The Office of Clinical Pharmacology concludes that the observed tocilizumab exposure in SJIA patients upon subcutaneous administration supports the extrapolation of the established efficacy of intravenous tocilizumab in SJIA patients.

The OCP recommends that the clinical pharmacology study submitted to sBLA 125472/S-031 addresses the PMR requirements and the respective sections of WR. This sBLA is approvable from a clinical pharmacology perspective.

X Suryanarayana M. Sista -S
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Primary Reviewer

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DCP2 Team Leader

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DPM Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The applicant submits the data from study WA28118 (JIGSAW 118), a phase Ib, pharmacokinetic/pharmacodynamic (PK/PD) study to confirm SC dosing regimens in sJIA patients and to assess the safety of SC TCZ in this same population. The study bridges to the IV TCZ in sJIA, study WA18221 (TENDER, sJIA in patients 2-17 years of age). Additional supporting data from the ongoing long-term extension (LTE) study WA29231 are also included in this application. These studies are described below in Table 9.

Table 9: Clinical Trials Supporting BLA 125472 Supplement 031

Trial Identity Study Center and Countries Status	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
WA28118 (JIGSAW 118) 26 centers Argentina (2 sites), Australia (1), Canada (3), France (1), Germany (3), Italy (1), Mexico (2), Russia (2), Spain (3), UK (1), US (7)	Phase Ib, 52-week, open-label, multicenter, PK/PD, and safety study	BW ≥30 kg: 162mg SC QW BW <30 kg: 162mg SC Q10D or Q2W (change in dosing regimen post-interim analysis)	PK endpoints: Serum TCZ concentration and population PK mode-predicted PK exposures (AUC, Cmax, Cmin) for the different dosing regimens at stead state Safety endpoints: AEs, SAEs, AESIs, clinical lab abnormalities	52 weeks	51 pts n=26 pts ≥30 kg n=25 pts <30 kg	Pediatric patients with sJIA, aged 1 to 17 years, who have had an inadequate response to NSAIDs and corticosteroids (CS)

Completed			PD endpoints: Serum IL-6 and sIL-6R levels, CRP, ESR, anti-TCZ Ab Exploratory efficacy endpoints: JADAS-71, inactive disease, clinical remission, CHAQ			
Supporting Studies						
WA18221 (TENDER) 43 centers Argentina (3 sites), Australia (3), Belgium (2), Brazil (2), Canada (2), Czech Republic (1), Germany (3), Greece (3), Italy (4), Mexico (2), Netherlands (1), Norway (1), Poland (1), Slovakia (1), Spain (2), UK (2), USA (10) *Completed*	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group, 2-arm study with 3 parts to evaluate efficacy and safety Part I: 12-wk, randomized, double-blind, placebo-controlled, parallel group, 2-arm (TCZ-active, PBO-control) period that evaluated the reduction of the signs and symptoms in pts with active sJIA at 12 wks	BW <30 kg: 12 mg/kg IV Q2W BW ≥30 kg: 8 mg/kg IV Q2W	<u>Part I</u> Primary endpoint: Proportion of patients with JIA ACR30 response at Week 12 and absence of fever (no diary temperature recording ≥37.5°C in preceding 7 days) Multiple secondary efficacy endpoints and additional PD, PK, safety, QOL assessments <u>Part II</u> • Safety in chronic administration • Effect on reduction/elimination	Part I: 12 wks Part II: 92 wks Part III: 3 yrs	112 pts randomized 2:1 TCZ:PBO n=75 on TCZ n=37 on PBO Part II: N=112 Part III: N=89	Pediatric pts ages 2-17 years with sJIA ≥6 months documented persistent activity with inadequate response to NSAIDs and CS due to toxicity or lack of efficacy

	Part II: single-arm (TCZ) OL extension to Wk 104 (2 yrs) to eval efficacy and safety endpts Part III: optional LTE phase (2 to 5 yrs) to assess long-term safety of TCZ		of CS <u>Part III</u> Long-term safety			
WA29231 *Ongoing*	Open-label extension of SC TCZ JIGSAW studies, WA28117 in pJIA and WA28118 in sJIA	TCZ 162mg SC at dosing interval according to JIA subtype and BW For sJIA, BW ≥30 kg: 162mg SC QW BW <30 kg: 162mg SC Q2W (Q10D prior to interim analysis)	Primary objective is long-term safety and efficacy of SC TCZ in pJIA and sJIA Exploratory objectives are long-term PK and PD of SC TCZ in pJIA and sJIA	Up to 5 years	Plan to enroll 96 subjects (48 from WA28117 and 48 from WA28118) From WA28118, actual N=38 as of data cutoff, Aug 11, 2017	Patients with pJIA or sJIA who completed either JIGSAW study and had an adequate response to SC TCZ (per investigator judgment)

7.2. Review Strategy

The efficacy and safety data from the open-label study WA28118 are limited and, thus, are supportive of the PK assessment already reviewed above. The review of efficacy and safety is primarily focused on study WA28118. Safety and efficacy are compared to data from study WA18221, the pivotal trial that supported approval of IV TCZ for sJIA. Additionally, a comparison with the LTE study WA29231 (specifically, subjects who extended from study WA28118) is summarized.

In general, this review is based on the applicant's results with commentary from the review team.

8 Statistical and Clinical and Evaluation

Review of Relevant Individual Trials Used to Support Efficacy

Study WA28118, the single study conducted to support this supplement, is presented in detail in Section 8.1. A brief synopsis of the other supportive trials (WA18221 and WA29231) is also provided below (Sections 8.2 and 8.3) prior to the review of the efficacy and safety data.

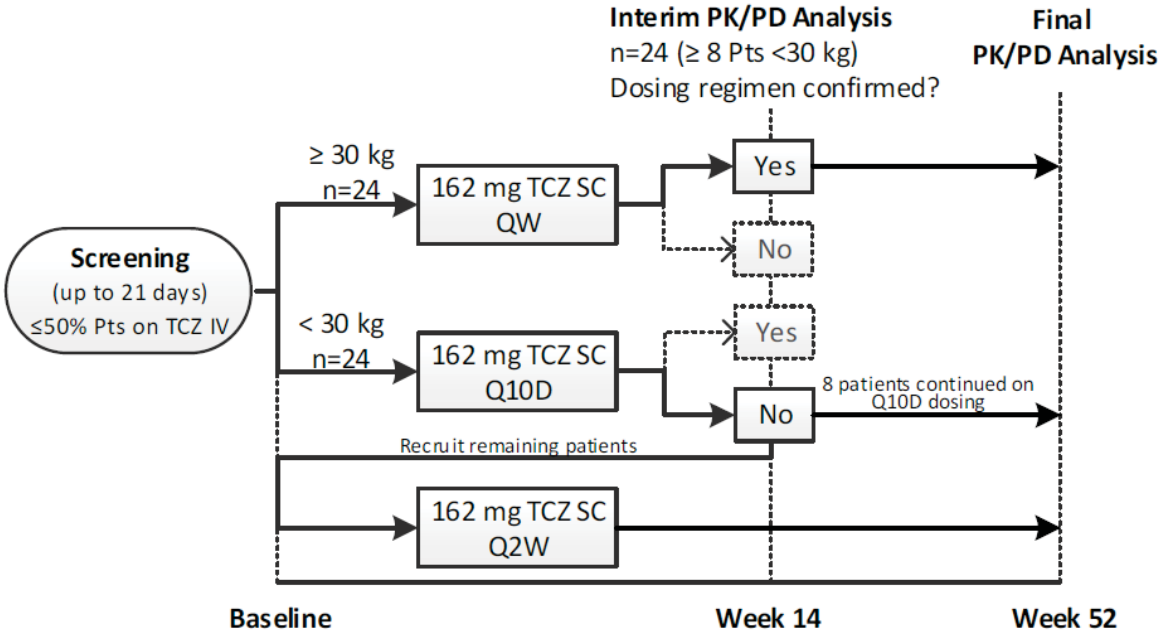
8.1. WA28118 (JIGSAW 118)

8.1.1. Study Design

Trial Design

Study WA28118 was a phase 1b, 52-week, open-label, multicenter, PK/PD, and safety study in pediatric patients with sJIA, aged 1 to 17 years-old (12 to 17 years-old for patients in Russia) to identify the SC dose regimen(s) with comparable PK/PD and safety profiles to the IV regimens established in study WA18221 (TENDER). Table 9 provides a general synopsis of study WA28118, and Figure 8 illustrates the study design.

Figure 8: WA28118 Study Schematic



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

Source: WA28118 Final CSR, Figure 1, dated December 2017, page 24.

The plan was to enroll 48 patients (actual N=51) of whom no more than 50% should have switched from IV to SC TCZ. Subjects weighing ≥30 kg (planned n=24, actual n=26) received 162mg SC every week (QW), and subjects weighing <30 kg (planned n=24, actual n=25) were initially dosed 162mg SC every 10 days (Q10D). A pre-specified interim analysis was conducted once approximately 24 subjects had completed the first 14 weeks of the study with at least 8 subjects weighing <30 kg (actual N=28; 8 subjects <30 kg and 20 subjects ≥30 kg) in order to confirm the initial dosing regimen. Further recruitment was put on hold until the conclusion of this interim analysis.

After review of the data from the interim analysis, the dosing regimen for subjects weighing <30 kg was changed from Q10D to every 2 weeks (Q2W). The QW dosing regimen for subjects weighing ≥30 kg remained unchanged. The study protocol was amended to reflect this updated dosing regimen. Subjects <30 kg who were enrolled prior to the interim analysis (n=8) were supposed to switch from the Q10D to Q2W dosing regimen. However, by the time the protocol amendment was approved, these patients had already completed the study. All new patients <30 kg enrolled after the interim analysis (n=17) did receive the new Q2W dosing regimen.

The protocol allowed for adjustment of the TCZ dosing interval if there were any changes in the body weight (BW) after Week 14.

In terms of concomitant therapy, subjects were allowed treatment with disease-modifying anti-rheumatic drugs (DMARDs), NSAIDs, and oral corticosteroids during the study at the discretion of the investigator. Other immunosuppressants (e.g., cyclosporine, cyclophosphamide, and biologic DMARDs [TNFα inhibitors and abatacept]) were not permitted.

Patient Population
Essentially, the patient population comprised of children between the age of 1 year (lowest age of 12 years in Russia) up to and including 17 years with a diagnosis of sJIA who had an inadequate response to NSAIDs and corticosteroids. Subjects included patients on IV TCZ with well-controlled disease (including patients who participated in study WA18221) and patients naïve to TCZ with active disease. Patients on IV TCZ at study initiation entered the study without a period of TCZ discontinuation and received the first dose of SC TCZ on the date that their next IV infusion would be due. Patients with well-controlled disease (specifically, JADAS-71 ≤ 3.8 without fever) on any other therapeutic agent were not eligible for inclusion in the study. Other significant inclusion/exclusion criteria are listed below.

Inclusion Criteria

- Diagnosis of sJIA according to the ILAR classification
- If the patient had received previous treatment with a biologic DMARD (e.g., etanercept, anakinra, abatacept, infliximab, adalimumab, canakinumab, rilonacept), there must be a

specific discontinuation period prior to the baseline visit (as outlined in the applicant's protocol).

- Patients participating in the study may have been either naïve to TCZ therapy or may have been switching from IV to SC. The total number of patients switching from IV TCZ must have accounted for no more than 50% of total subjects. To account for the baseline TCZ concentrations in these patients, information on the last 4 IV TCZ infusions prior to baseline was collected.
    - Patients <30 kg could choose to switch to commercially available IV TCZ pending approval of the amended protocol (after the interval analysis) and were allowed to stay in the study on the new dosing regimen following approval.
- Reproduction
    - For female patients of reproductive potential (unless surgically sterile with absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of TCZ
    - For male patients of reproductive potential: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of TCZ.
- Written informed consent for participation
- Parent/guardian written agreement to comply with the protocol

<u>Exclusion Criteria</u>

- Prior discontinuation of IV TCZ because of inadequate clinical response or safety events (including hypersensitivity)
- Poorly controlled disease despite treatment with IV TCZ
- Participation in another interventional clinical trial within past 30 days or 5 serum half-lives of the investigative medication
- Patients who are wheelchair-bound or bedridden
- Any other autoimmune, rheumatic disease or overlapping syndrome other than sJIA
- Lack of recovery from recent surgery or an interval of <6 weeks since surgery at the time of the screening visit
- Females who were pregnant, lactating, or intended to become pregnant
- Any significant concurrent medical or surgical condition that would have jeopardized the patient's safety or ability to complete the study
- Infection
    - HIV or other acquired or congenital immunodeficiency
    - Any active acute, subacute, chronic, or recurrent bacterial, viral, or systemic fungal infection or any major episode of infection requiring hospitalization or treatment with antibiotics immediately before screening (IV 4 weeks before or oral 2 weeks before)

  - History of atypical tuberculosis (TB) or active TB requiring treatment within 2 years prior to screening
  - Positive PPD (or Quantiferon gold) at screening unless treated with anti-TB therapy for at least 4 weeks prior to study drug and negative CXR within 6 weeks of screening
  - History of reactivation or new onset of systemic infection (e.g., herpes zoster or EBV) within 2 months of screening
  - Hepatitis B surface antigen or hepatitis C antibody positivity or chronic viral or autoimmune hepatitis
- History of concurrent serious gastrointestinal (GI) disorders (e.g., ulcer or IBD [Crohn's or ulcerative colitis], or other symptomatic lower GI conditions)
- History of or current cancer or lymphoma
- Uncontrolled diabetes mellitus with elevated HgbA1c
- MAS within 3 months of screening
- Abnormal baseline laboratory values for serum creatinine, AST/ALT, Total bilirubin, platelet count, hemoglobin, white blood cell (WBC) count, neutrophil count (exact parameters specified in the protocol)
- Prior stem cell transplant at any time

Study Endpoints

The primary objectives of this study were PK, PD, and safety. Efficacy was an exploratory objective. Thus, based on these objectives, the following endpoints were assessed.

PK assessments: Serum TCZ concentration and population PK model-predicted PK exposures (area under the concentration-time cure [AUC], maximum and minimum plasma concentration [Cmax and Cmin] for the different dosing regimens at steady state.

PD assessments:
- Serum IL-6 and sIL-6R levels, CRP, ESR
- Incidence of anti-TCZ antibodies

Safety assessments:
- Incidence of adverse events (AEs, including local injection site reactions) and serious AEs (SAEs)
- Incidence and severity of adverse events of special interest (AESIs)
- Incidence and severity of clinical laboratory abnormalities

Exploratory Efficacy endpoints:
- Juvenile Arthritis Disease Activity Score (JADAS)-71
  JADAS-81 is derived using the following core set components:

  - Physician's global assessment of disease activity, using a 100mm visual analog scale (VAS)
  - Patient/parent's global assessment of overall well-being (100mm circle VAS)
  - Normalized ESR
    - If ESR is ≤ 20 mm/hr, then set to 0.
    - If ESR > 20 mm/hr and < 120 mm/hr, then apply formula, ESR-20/10 mm/hr
    - If ESR ≥ 120 mm/hr, then set to 10
  - Number of joints (total 71) with active arthritis

  The initial 3 components have a score range from 0 to 10, and the final component has a score rage from 0 to 71. Thus, the overall JADAS-71 range is 0 to 101.

- Inactive disease
  Subjects must satisfy all of the following criteria in order to achieve "inactive disease."
  - Number of joints with active disease = 0
  - Absence of active uveitis
  - No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA
  - Normal ESR (<20 mm/hr)
  - Physician global assessment of disease activity VAS ≤ 10
  - Duration of morning stiffness ≤ 15 minutes

  If there were any missing core components, the sponsor utilized LOCF (last observation carried forward) to derive an assessment of inactive disease.

- Clinical remission
  Clinical remission was defined as inactive disease for a minimum of 6 continuous months irrespective of DMARD, NSAID, or corticosteroid use.

- Childhood Health Assessment Questionnaire (CHAQ)
  The CHAQ consists of 30 questions referring to 8 domains (dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities) plus the patients (or parents) global evaluation of their (child's) current disease activity using a 100mm VAS and a pain score measured on a 100mm VAS. Each domain has at least 2 component questions, and there are 4 possible responses (0 [without any difficulty] to 3 [unable to do]).

  Functional ability is assessed using the Disability Index of the CHAQ (CHAQ-DI), which is the sum of the domain scores divided by the number of domains that have a non-missing score. The overall CHAQ-DI ranges from 0 (best) to 3 (worst).

Statistical Analysis Plan

As this is an open-label, uncontrolled study, all statistical analyses were descriptive in nature. Presentation of categorical variables included the number and percentage of patients, whereas presentation of continuous variables included summary statistics including means, medians, ranges, and standard deviations.

Sample size:
The applicant reports using the methodology endorsed by Wang, et al. in "Clarification on precision criteria to derive sample size when designing pediatric PK studies" to determine the size in this study. An initial same size of approximately 48 patients would allow targeting a power of at least 80% to have the 95% confidence interval (CI) within 60% and 140% of the population mean estimates for the PK parameters in the age group to be studied. The population mean estimates for the PK parameters were obtained from a population PK model developed using data from study WA18221.

Analysis populations:

- PK/PD Population
  The PK/PD population included all patients enrolled and adherent to the protocol. Patients were excluded from the PK/PD analysis population if they significantly violated the inclusion or exclusion criteria, deviated significantly from the protocol, or if data were unavailable or incomplete, which may influence the PK/PD analysis. Per the applicant, all decisions regarding exclusions were documented and completed prior to database closure.

- Safety Population
  The safety population included all subjects who received at least 1 dose of treatment and had at least 1 post-dose safety assessment.

- Intent-to-Treat (ITT) Population
  The ITT population was utilized for all exploratory efficacy descriptive analyses and included all patients enrolled who received at least 1 dose of study drug.

Protocol Amendments

The original protocol was dated February 13, 2013. Since that time, the applicant amended the protocol 5 times.

- Protocol Amendment, Version 2 (March 19, 2013)
  - [redacted] (b) (4) was removed as a PRO tool for legal reasons and was replaced with the CHAQ functional ability instrument.
  - The immunogenicity testing requirements were updated for patients who withdrew due to hypersensitivity or anaphylaxis.

  - Dose interval changes for subjects whose BW changed (above or below 30kg) was clarified.
- Protocol Amendment, Version 3 (May 8, 2013, Russia)
  - The age range in the Inclusion Criteria was changed to 12 to 17 years in Russia only.
- Protocol Amendment, Version 4 (August 5, 2013)
  - The number of patients switching from IV to SC TCZ was limited to no more than 50% of the total number of subjects. Information on the prior 4 IV infusions for patients making this switch should also be collected.
- Protocol Amendment, Version 5 (March 2, 2015)
  - Following the interim analysis, the dose for subjects <30 kg was switched from Q10D to Q2W. This change would apply to newly enrolled subjects as well as those who were already enrolled and had received the Q10D regimen.
  - The applicant notes that this version of the protocol was finalized but not submitted to study sites or Health Authorities, as further updates were also being identified.
- Protocol Amendment, Version 6 (June 23, 2015)
  - The change in the dosing regimen for subjects <30 kg was again made in this version. This is the version that was submitted to Health Authorities and study sites.
  - Other minor changes were also included in this amendment.

Reviewer's Comment: The open-label study design was reasonable for this PK bridging study to evaluate SC TCZ in sJIA. Additionally, the study design satisfied the requirements of Study 3 of the Pediatric Written Request. As an open-label study, interpretation of the safety and efficacy is limited but can be used to support the PK analysis.

8.1.2. Study Results

Compliance with Good Clinical Practices

The applicant notes that all studies in the TCZ SC sJIA development program were conducted or are being conducted according to the principles of Good Clinical Practice and in compliance with the Declaration of Helsinki and its amendments. The study protocol addressed the ethics and study conduct in the following areas: compliance with laws and regulations; informed consent procedures; Institutional Review Boards (IRBs) and/or Ethics Committee (ECs) approval; data quality assurance and data collection and management; and audits and GCP compliance. Instructors were trained according to applicable applicant SOPs. Roche and the investigators strictly adhered to the stated provisions in these guidelines, and this was documented by the investigator's signature of agreement on the protocol. Approval from the IRB/EC was obtained before study start and was documented in a letter to the Investigator. Roche also obtained approval from the relevant Competent Authority prior to starting the study. Protocol amendments were prepared by the applicant and were submitted to the IRB/EC and to Regulatory Authorities, and their approval was required before any changes were made.

Additionally, the Roche Clinical Quality Assurance group or designee conducted audits at 2 investigator sites in study WA28118. Per the applicant, no critical audit findings were observed, and, for all audit findings, appropriate corrective and preventive actions were undertaken.

Financial Disclosure

See Section 18.2 for detailed financial disclosure information for study WA28118.

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*. There were 197 total investigators involved in study WA28118. Two investigators ((b) (6) [principal investigator] and (b) (6) [sub-investigator]), both from (b) (6), had financial information to disclose. Both investigators received payments in excess of $25,000 for services including consultation, speaker bureau, site investigator, and advisory board. A total of (b) (6) patients were recruited at their site for study (b) (6).

The applicant provided the following details regarding steps taken to minimize potential bias from these 2 investigators.

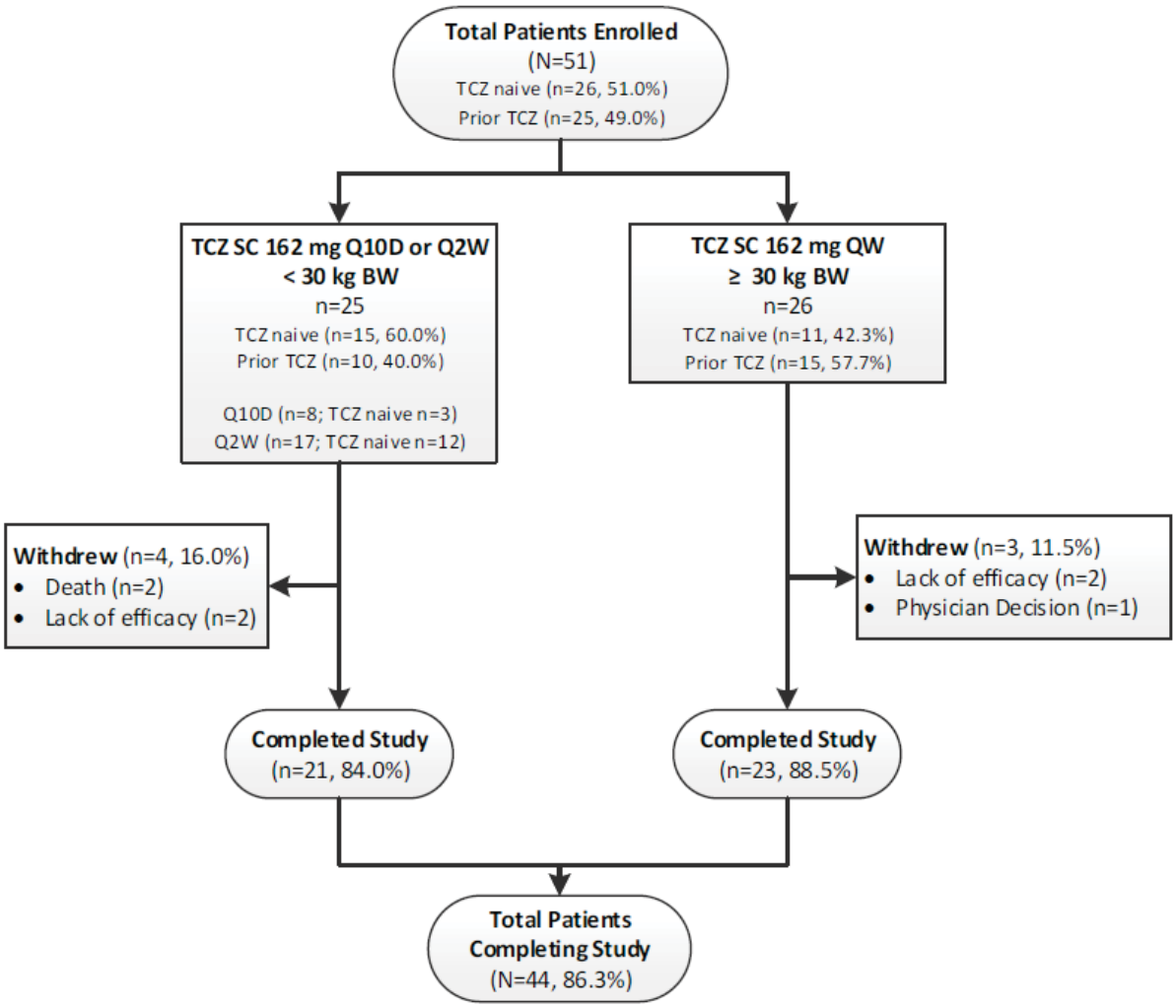
- The applicant clarified that the work done on this study was done as part of a contract between (b) (6) and Hoffmann-La Roche. Accordingly, no direct funding to (b) (6) occurred as a result of their work on the study. As the PI, (b) (6) was responsible for the overall function all study-related personnel on this site, and both (b) (6) were involved in the review of inclusion/exclusion criteria for patients and the performance of MD specific study assessments. They were not involved in consenting the patient or drawing of blood. The site study clinical research associate (CRA) performed all consenting with the MD absent in order to avoid undue influence on the family. Additionally, the completion of any patient/parent reported outcomes were done independently without (b) (6) being present. Both investigators had no role in distribution of study drug.
- A second contract oversaw the role of the (b) (6) for the assessment of data from study visits from all sites to assess response and flare in the patient at the study visits. (b) (6) is the Chairman of the (b) (6), and (b) (6) is the Scientific Director. The applicant confirmed that these (b) (6) assessments were done in accordance with protocol and by the applicant's coordinating center CRAs using standard operating procedures of the (b) (6) These assessments were done by the coordinating center CRA independently of (b) (6) and all communication with the site was done by the coordinating center CRAs without input or influence from (b) (6).

Reviewer Comment: Two investigators at the same clinical site had financial disclosures. Given the small number of patients recruited at the site (only (b)(6) subjects) and the steps taken to address the financial arrangements between the investigators and the applicant, these financial disclosures do not raise any concerns and do not affect the approvability of this application.

Patient Disposition

Fifty-seven patients were screened, and a total of 51 enrolled into the study and received TCZ. Twenty-five subjects weighed <30 kg, of whom 8 received 162mg SC Q10D (prior to interim analysis) and 17 received 162mg SC Q2W (after interim analysis). Figure 9 displays the disposition of the enrolled subjects.

Figure 9: WA28118 Patient Disposition



Source: WA28118 Final CSR, Figure 2, dated December 2017, page 45.

The study protocol required that <50% of subjects could have previously been treated with IV TCZ. Of the enrolled subjects, 51% (n=26) were TCZ naïve, and 49% (n=25) had prior TCZ experience. Twenty-five subjects (40.0%) were categorized into the <30 kg group, and 26 subjects (57.7%) started the study ≥30 kg. One patient, initially weighing <30 kg, switched from Q10D dosing to QW dosing after Day 218 after an increase in body weight ≥30 kg.

Seven subjects (4 in <30 kg group and 3 in the ≥30 kg group) withdrew early from the study. Most subjects withdrew due to lack of efficacy (2 subjects in both weight groups). There were 2 deaths in the <30 kg group, and 1 subject in the ≥30 kg group was withdrawn by the physician due to persistently low neutrophil counts. These early withdrawals will be described further under the review of safety.

The study ended on June 13, 2017, when the last participating subject completed the last scheduled visit. A total of 44 subjects (86.3%) completed the study with similar proportions in each weight group (84.0% in <30 kg group and 88.5% in ≥30 kg group).

For the purposes of this review, the safety population, ITT population, and the PK/PD population included all 51 subjects enrolled into the study.

Protocol Violations/Deviations

Seven major protocol deviations (in 6 subjects, 2 in the <30 kg group and 4 in the ≥30 kg group) occurred in study WA28118. None were considered significant enough to be excluded from the PK/PD population.

- 3 protocol deviations in the "medication" category (administration of prohibited vaccine [2] and administration of incorrectly stored drug)
- 2 protocol deviations in the "exclusion criteria" category (missing laboratory values prior to randomization and missing bilirubin value at screening)
- 2 in the "procedural" category (PK sample not taken at single time point and no re-consent of updated version of the ICF)

Table of Demographic Characteristics

Table 10 displays the baseline demographics of subjects enrolled in study WA28118 by dosing regimens. The majority of subjects were female and Caucasian overall. Given the dosing regimens were weight-tiered, it is anticipated that the age, weight, and height of subjects would differ for both groups. In the <30 kg group, the mean age was 5 years, and the mean weight was 18.7 kg. In the ≥30 kg group, the mean age was 13 years, and the mean weight was 51.7 kg.

Table 10: WA28118 Demographics and Patient Characteristics at Baseline

Demographic Parameters	Tocilizumab (N=51)	
	TCZ 162mg SC Q10D or Q2W (< 30 kg) (N=25) n (%)	TCZ 162mg SC QW (≥ 30 kg) (N=26) n (%)
Sex		
Male	12 (48.0%)	10 (38.5%)
Female	13 (52.0%)	16 (61.5%)
Age		
Mean years (SD)	5.1 (3.2)	13.3 (3.2)
Median (years)	5.0	14.0
Min - max (years)	1-13	6-17
Weight		
Mean kg (SD)	18.7 (5.7)	51.7 (13.1)
Median (kg)	19.6	51.7
Min - max (kg)	9.2-27.2	30.0-73.2
Height		
Mean cm (SD)	105.9 (18.2)	155.3 (14.1)
Median (cm)	104.5	154.8
Min - max (cm)	79.0-136.5	127.7-175.6
Race		
White	20 (80.0%)	21 (80.8%)
Black or African American	1 (4.0%)	0
Asian	0	1 (3.8%)
American Indian or Alaska Native	1 (4.0%)	0
Other[1]	3 (12.0%)	4 (15.4%)
Ethnicity		
Hispanic or Latino	5 (20.0%)	1 (3.8%)
Not Hispanic or Latino	19 (76.0%)	20 (76.9%)

[1] Race of "Other" includes Other, Multiple, and Unknown.
Source: WA28118 Final CSR, Table 4, dated December 2017, page 48-49.

The applicant also evaluated the demographics of subjects based on TCZ status, i.e., those who were naïve to TCZ vs. subjects who switched from IV TCZ. The baseline characteristics were similar between these 2 categories with proportions similar to the overall safety population.

Three subjects were less than 2 years-old.

- Subject (b) (6) a 17-month-old boy with a BW of 10.3 kg on Q10D regimen
- Subject a 19-month-old girl with a BW of 11.0 kg on Q2W regimen
- Subject a 22-month-old girl with a BW of 11.5 kg on Q2W regimen

The applicant clarified that these subjects who were < 2 years old were all at the 50th percentile according to the WHO weight-for-age standards. The applicant did note, however, that there was 1 subject who was less than 10 kg at baseline.

- Subject (b) (6): a 25-month old girl with a BW of 9.2 kg on Q10D regimen

Efficacy and safety for these 4 subjects will be highlighted in the Subpopulation analyses under Sections 9.1 and 10, respectively.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Important disease characteristics are summarized for the <30 kg and ≥30 kg dosing regimens in Table 11. In the overall safety population, subjects <30 kg had more active disease by all measures than subjects in the higher weight group. This discrepancy may be related to the younger age of the lighter weight group. It is also important to note that this difference was most prominent in subjects who were naïve to TCZ, as subjects who were previously being treated with IV TCZ were essentially well controlled at baseline.

Table 11: WA28118 Baseline Disease Characteristics

	Tocilizumab (N=51)	
	TCZ 162mg SC Q10D or Q2W (< 30 kg) (N=25) n (%)	TCZ 162mg SC QW (≥ 30 kg) (N=26) n (%)
# of Active Joints		
Mean (SD)	7.5 (10.3)	3.5 (6.0)
Median	3.0	1.0
Min - max	0-32	0-29
Patient/Parent Global Assessment VAS (0-100 mm)		
Mean (SD)	35.6 (30.3)	25.3 (29.7)
Median	22.0	7.5
Min - max	0-87	0-87
Physician Global Assessment VAS (0-100 mm)		
Mean (SD)	31.3 (26.3)	20.1 (23.0)
Median	30.0	11.0
Min - max	0-90	0-73
CHAQ-DI Score		
Mean (SD)	0.9 (0.9)	0.6 (0.9)
Median	0.4	0
Min - max	0-2.5	0-2.65
Erythrocyte Sedimentation Rate (mm/hr)		
Mean (SD)	24.1 (28.7)	15.9 (22.7)
Median	10.0	5.0
Min - max	0-120.0	0-90.0
C-Reactive Protein (mg/L)		
Mean (SD)	24.8 (28.7)	10.9 (27.8)
Median	3.3	0.3
Min - max	0.2-186.0	0.2-117.0
JADAS-71 (0-101)		
Mean (SD)	15.5 (15.8)	8.7 (10.8)
Median	10.5	5.5
Min - max	0-53.1	0-46.9
Previous conventional DMARD use	14 (56.0%)	24 (92.3%)
Previous biologic DMARD use	14 (56.0%)	23 (88.5%)
Previous MTX use	13 (52.0%)	20 (76.9%)
Background MTX use	13 (52.0%)	14 (53.8%)
Background oral corticosteroid use	20 (80.0%)	12 (46.2%)

Source: WA28118 Final CSR, Table 4, dated December 2017, page 49-50.

Table 12 shows some of the baseline disease characteristics by TCZ status. In the subjects who were previously treated with IV TCZ, there was a small difference between the dosing regimens, but, overall, the disease measures showed good control for all subjects on IV TCZ.

Table 12: Baseline Disease Characteristics by TCZ Status (WA28118)

	TCZ Naïve (N=26)		Prior TCZ (N=25)	
	TCZ 162mg SC Q10D or Q2W (< 30 kg) (N=15) n (%)	TCZ 162mg SC QW (≥ 30 kg) (N=11) n (%)	TCZ 162mg SC Q10D or Q2W (< 30 kg) (N=10) n (%)	TCZ 162mg SC QW (≥ 30 kg) (N=15) n (%)
# of Active Joints				
Mean (SD)	11.6 (11.6)	6.6 (8.1)	1.3 (1.8)	1.2 (2.2)
Median	5.0	5.0	0.5	0
Min - max	1-32	0-29	0-5	0-8
CHAQ-DI Score				
Mean (SD)	1.3 (0.9)	0.8 (1.0)	0.3 (0.4)	0.5 (0.8)
Median	1.5	0.3	0.1	0
Min - max	0-2.5	0-2.6	0-1.4	0-2.0
C-Reactive Protein (mg/L)				
Mean (SD)	41.0 (50.5)	25.4 (39.1)	0.5 (0.5)	0.2 (0.1)
Median	27.5	6.7	0.2	0.2
Min - max	0.9-186.0	0.4-117.0	0.2-1.5	0.2-0.6
JADAS-71 (0-101)				
Mean (SD)	23.6 (15.6)	15.9 (12.4)	3.2 (3.3)	3.5 (5.2)
Median	15.1	13.2	2.5	1.0
Min - max	7.7-53.1	1.9-46.9	0-10.5	0-17.8

Source: WA28118 Final CSR, Table 4, dated December 2017, page 49-50.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Table 11 also describes previous and baseline therapy. More subjects in the higher weight group had previous treatment with conventional DMARDs, biologic DMARDs, and MTX. This is again consistent with this group being older and likely having tried more therapy through the years. In terms of background use of MTX, this was similar between both dosing regimens, whereas more subjects in the lighter weight group (80%) compared to the higher weight group (46.2%) was on background oral corticosteroids. NSAIDs were also used concomitantly by 82.4% of patients at similar proportions for both weight groups.

Approximately 50% of subjects in both dosing regimens (48% in the BW <30 kg group and 53.8% in the BW ≥30 kg group) completed all dose of TCZ in the study. Most subjects missed 1-3 doses of TCZ.

Efficacy Results

The efficacy data from study WA28118 are limited given this is an open-label study. As noted in above, the efficacy endpoints were exploratory. Efficacy results for study WA28118 are briefly summarized below in Section 9.1, and they will be reviewed in comparison to the data from the pivotal study which led to the approval of IV TCZ for sJIA, i.e., the study data to which this study bridges. Additionally, the efficacy data of subjects from WA28118 who entered the LTE will also be briefly summarized alongside the data from WA28118.

8.2. WA18221 (TENDER)

Trial Design

Table 21 provides a synopsis of study WA18221, the 5-year, 3-part pivotal trial that supported approval of IV TCZ for sJIA (ages 2 years and older). Enrolled subjects had sJIA with persistent activity and an inadequate response to NSAID and corticosteroids. Figure 10 illustrates the study design of study WA18221.

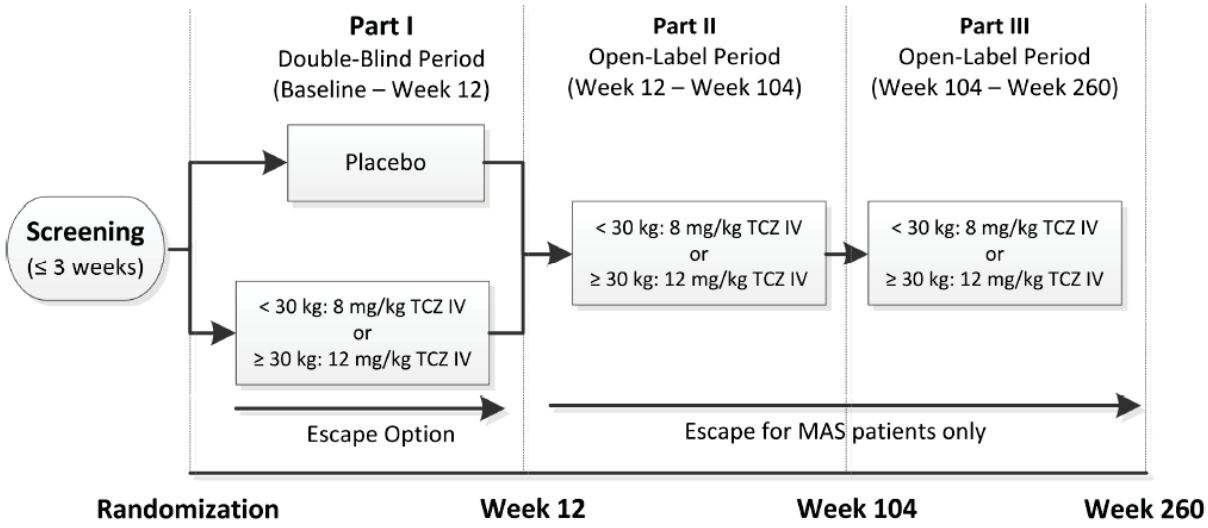
Part I was the 12-week, placebo-controlled, double-blind, and randomized phase. Patients weighing <30 kg were randomized 2:1 to receive either TCZ 12 mg/kg IV Q2W or PBO IV Q2W. Patients weighing ≥30 kg were randomized 2:1 to receive either TCZ 8 mg/kg IV Q2w or PBO IV Q2W. Patients had the option to escape to open-label TCZ in case of high disease burden. The primary objective of Part I was assessment of efficacy and short-term safety of IV TCZ versus PBO in combination with stable ongoing therapy in patients with sJIA. Subjects who completed the first 12 weeks of Part I or who escaped (and were benefiting from IV TCZ) had the option to enter Part II.

Part II was a single-arm, open-label, 92-week treatment phase. Subjects who received IV TCZ in Part I continued the same dose, and subjects on PBO in Part I were initiated on IV TCZ at the appropriate weight-based dose. If there was a persistent change in BW (over at least 3 consecutive visits), subjects could change dosing regimens. Reductions in corticosteroids, MTX, and NSAIDs were also permitted based on pre-specified criteria. The primary objectives of Part II were evaluation of safety of chronic TCZ and assessment of the effect of TCZ on reduction/elimination of corticosteroids. Subjects who completed Part II were eligible for Part III.

Part III consisted of a single-arm, open-label, 3-year treatment phase. Essentially, TCZ dose, allowance for changes in dose based on weight, and reduction in concomitant medications were the same as described for Part II. In addition, this part included an optional alternative TCZ dosing schedule (i.e., less frequent infusions [Q3W or Q4W] or no TCZ infusions) based on

clinical response and safety status. The primary objective of Part III was assessment of long-term safety of IV TCZ.

Figure 10: WA18221 Study Schematic



MAS = Macrophage activation syndrome.

Source: BLA 125472/031 Summary of Clinical Efficacy, submitted March 2018, page 11.

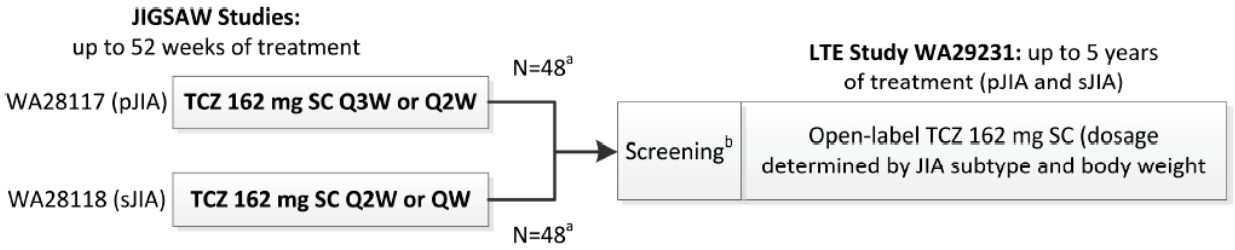
The LTE data cut (May 10, 2010) for study WA18221 occurred when at least 50 subjects had 1 year of TCZ treatment (through Part II). Thus, the efficacy and safety data through the LTE data cut would be most comparable to the data from study WA28118 and will be used in this supplement to support the data from WA28118. In actuality at the time of the LTE data cut, 87 subjects (out of 112) completed at least 1 year of IV TCZ with a median duration of exposure of 1.14 years.

8.3. WA29231 (LTE study of WA28117 and 28118)

Trial Design

Table 9 presents a synopsis of study WA29231, the ongoing, open-label extension of the TCZ SC JIGSAW studies (WA28117 for pJIA and WA28118 for sJIA). Figure 11 illustrates the study design. Subjects who completed studies WA28117 or WA28118 and had an adequate response to SC TCZ (per investigator's judgment) are eligible for this study. The plan is to enroll approximately 96 subjects (50% from each study), who would continue to receive the same dose of SC TCZ according to JIA subtype and BW. The dosing interval can be adjusted for changes in body weight. The primary objective of the ongoing study is assessment of the long-term safety and efficacy of SC TCZ in children with pJIA and sJIA. The exploratory objective includes exploration of long-term PK and PD of SC TCZ.

Figure 11: WA29231 Study Schematic



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

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

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

Source: BLA 125472/031 Summary of Clinical Efficacy, submitted March 2018, page 12.

At the time of data cutoff (August 11, 2017), there were 38 subjects in study WA29231 who had extended from study WA28118. Efficacy and safety data from these subjects will be reviewed to support the data from study WA28118.

9 Integrated Review of Effectiveness

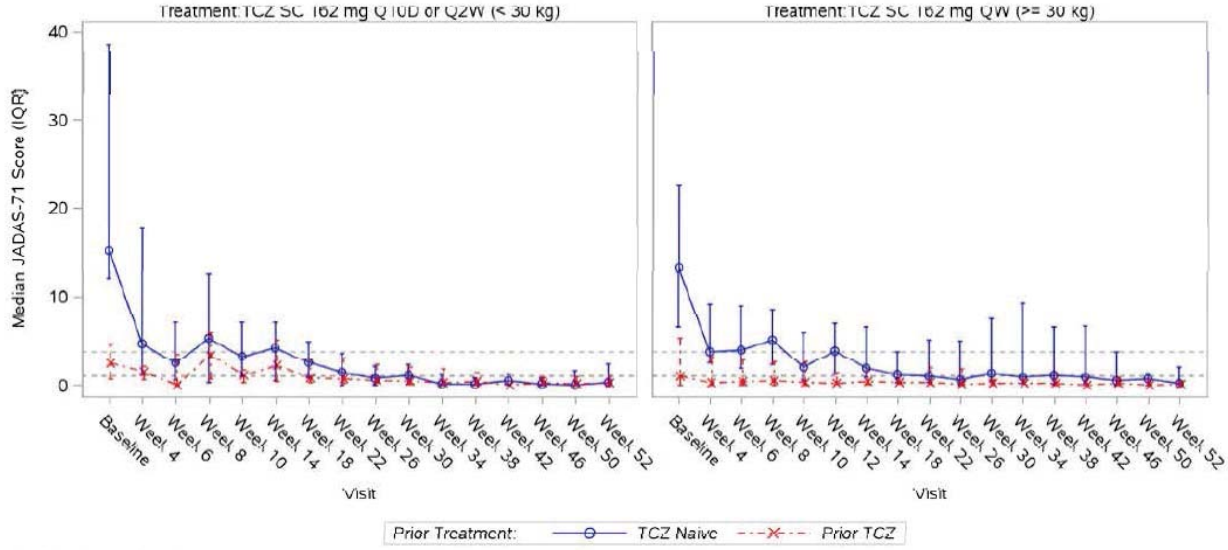
9.1. Assessment of Efficacy Across Trials

Exploratory Endpoints

Efficacy assessments in Study WA28118 were exploratory and, thus, supportive of the PK analyses already reviewed in Section 6 above.

JADAS-71 was one of the composite scores monitored over the course of the study. Figure 12 shows the median JADAS-71 by visit for each dosing regimen. For both doses, the TCZ naïve subjects started with active disease, which then reduced over time to a JADAS-71 <1.0 (which is consistent with inactive disease) by Week 26. These subjects were then maintained at this low level. Subjects who were previously treated with IV TCZ started with a low JADAS-71. After switching to SC TCZ, the JADAS-71 score further decreased to inactive disease (<1.0) by Week 18 and also remained low over time.

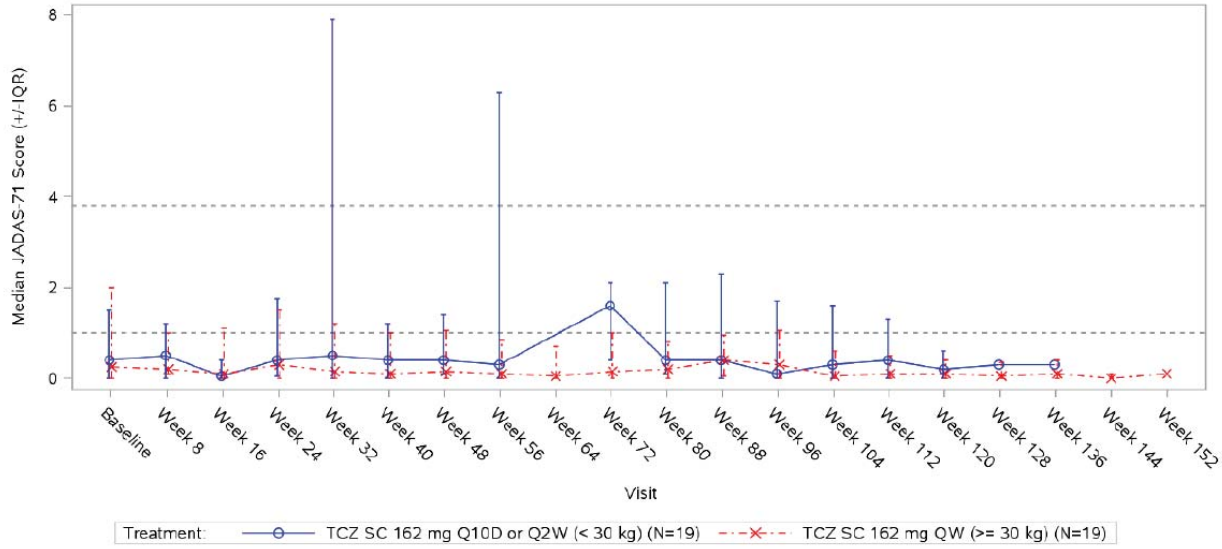
Figure 12: Median JADAS-71 Score (0-101) by Visit and by Prior TCZ Use (WA28118)



Source: WA28118 Final CSR, Figure 8, dated December 2017, page 102.

Figure 13 shows the median JADAS-71 over time in the LTE study WA29231. Data from this study are event more limited, as there are only 38 subjects from WA28118 who entered the LTE at the time of data cutoff. From the limited data, it appears that JADAS-71 values remained low (less than minimal disease activity, <3.8) and close to inactive disease (<1.0). The applicant points out that, by Week 24 in the <30 kg group, only 8 subjects remained in the study and that, by Week 136 in the ≥30 kg group, only 7 subjects were in the study. Thus, it is even more difficult to draw any conclusions at those points in the study.

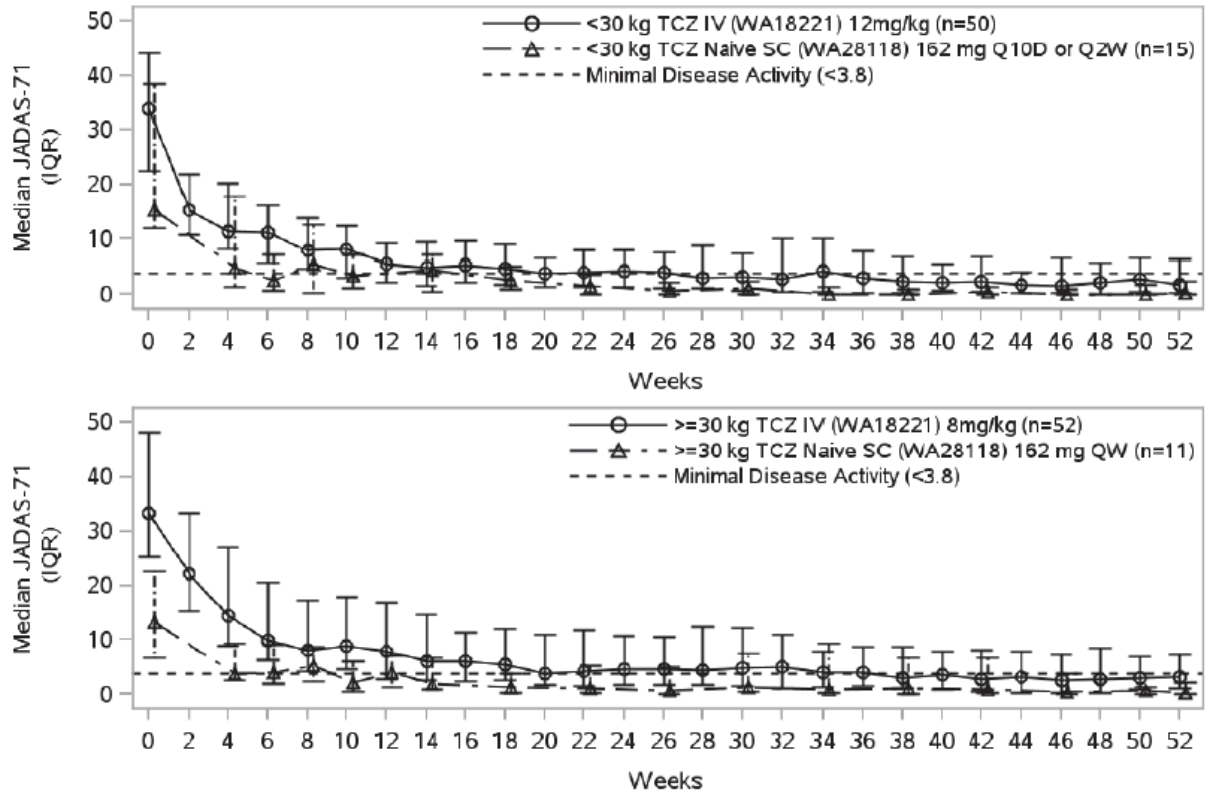
Figure 13: Median JADAS-71 Values by Visit (LTE WA29231)



Source: BLA 125472/031 Summary of Clinical Efficacy, Figure 13, submitted March 2018, page 39.

Lastly, Figure 14 compares the median JADAS-71 values of the TCZ naïve subjects in study WA28118 and the all TCZ group in study WA18221 (IV TCZ in sJIA study, all without previous TCZ experience). Each graph reports the 2 weight groups for dosing, <30 kg and ≥30 kg. Again, these comparisons are limited because there was no control in study WA28118. The subjects in study WA28118 (SC TCZ) started with less active disease (lower baseline JADAS-71), thus, the potential reason why subjects in study WA18221 took a few more weeks to reach minimal disease activity. However, the overall trend in JADAS-71 over 52 weeks was similar for SC TCZ and IV TCZ in sJIA.

Figure 14: Comparison of Median JADAS-71 through Week 52 (WA28118 and WA18221)



Source: BLA 125472/031 Summary of Clinical Efficacy, Figure 16, submitted March 2018, page 51.

CHAQ-DI is a measure of functional ability. The TCZ naïve subjects had a greater improvement in CHAQ-DI than Prior TCZ subjects, as the Prior TCZ subjects had a low CHAQ-DI at baseline. In assessing the proportion of subjects with a minimally clinically important improvement in CHAQ-DI scores from baseline (defined as > 0.13 improvement), the greatest improvement was noted in the TCZ naïve <30 kg group (90.0%) compared to the TCZ naïve ≥30 kg group (54.5%).

The proportion of subjects who achieved "Inactive Disease" also gradually increased over time for all subjects, regardless of TCZ status and baseline BW. However, the TCZ naïve ≥30 kg group had the smallest increase over time with just 54.5% with inactive disease at Week 52, whereas

76.9% of the TCZ naïve <30 kg group, 87.5% of the Prior TCZ <30 kg group, and 100% of the Prior TCZ ≥30 kg group were defined as having inactive disease at Week 52.

Clinical Remission was another exploratory efficacy assessment. The TCZ naïve subjects had a greater increase in subjects with clinical remission over time. By Week 52, 50.0% of TCZ naïve subjects and 75.0% of Prior TCZ subjects met the criteria for clinical remission.

Subpopulations

As efficacy was exploratory, no formal subpopulation analyses were performed. Efficacy of the 2 dosing regimens (<30 kg and ≥30 kg) was assessed, as already described above.

The applicant did provide a separate analysis of the efficacy of the 3 subjects < 2 years and the 1 subject weighing < 10 kg (Table 13). The JADAS-71 was low for the 3 subjects who were <2 years even at baseline, as they were previously treated with IV TCZ. After switching to SC TCZ, JADAS-71 remained low through Week 52. JADAS-71 also lowered and stayed low for the subject <10 kg.

Table 13: JADAS-71 Result of Patients < 2 Years Old and Lightest Weight (< 10 kg) in WA28118

Subject ID	BW	TCZ Status	JADAS-71			
			Baseline	Week 10	Week 26	Week 52
< 2 years old						
(b) (6)	10.3 kg	Prior TCZ	1.0	1.1	0.6	0.4
	11.0 kg	Prior TCZ	0.0	0.0	0.0	0.0
	11.5 kg	Prior TCZ	0.8	0.3	0.4	0.0
< 10 kg BW at baseline						
(b) (6)	9.2 kg	TCZ naive	12.0	0.4	0.2	0.0

Source: BLA 125472/031 Clinical Overview, Table 7, submitted March 2018, page 48.

9.2. Integrated Assessment of Effectiveness

The efficacy assessments were exploratory in this open-label, uncontrolled study (WA28118). Thus, interpretation of effectiveness is limited but can be supportive of the PK assessments/bridge to IV TCZ for the treatment of sJIA. The JADAS-71 (and its components), CHAQ-DI, "inactive disease" assessment, and "clinical remission" assessment all showed that there was a trend toward improvement with the use of SC TCZ in sJIA.

To further support this open-label data, the applicant compares these assessments with the LTE study (which includes 38 subjects from study WA28118 at the time of data cutoff) and with the IV TCZ for sJIA study. Efficacy, particularly with JADAS-71, appeared to be maintained through the LTE. Additionally, the trend of improvement to minimal disease activity was similar to what was seen in the IV study.

Lastly, the applicant highlights the 3 subjects who were less than 2 years-old in study WA28118. All 3 subjects were previously treated with IV TCZ and, thus, entered the study in good disease control, which was maintained with SC TCZ. It is difficult, however, to make any conclusions based on the experience of 3 subjects. The only conclusion perhaps is that the data are consistent with the rest of the efficacy data, which support the PK bridging strategy.

10 Review of Safety

10.1. Safety Review Approach

The safety review is based on the open-label data from study WA28118. Thus, the safety data are limited but serve to support the primary PK objective of this submission. Data are analyzed with a focus on what is already know about TCZ, particularly the known risks of the approved IV dosing regimen for sJIA. Thus, as with the efficacy review, the data from WA28118 are supported by safety from the pivotal trial of IV TCZ for sJIA (study WA18221 through the LTE cutoff, which was roughly 52 weeks of therapy) and from the SC TCZ LTE study in pJIA and sJIA (study WA29231).

10.2. Review of the Safety Database

Overall Exposure

Table 14 displays the overall exposure to TCZ in study WA28118. The mean study and treatment duration was 0.9 year for both dosing regimens. The median study and treatment duration was 1.0 year. Because of the different dosing intervals for the 2 BW groups, it is expected that subjects in the ≥30 kg group received approximately twice as many doses of TCZ than the <30 kg group.

Table 14: Summary of Exposure to Study Drug (WA28118)

	TCZ 162mg SC Q10D or Q2W (< 30 kg) (N=25)	TCZ 162mg SC QW (≥ 30 kg) (N=26)	All TCZ (N=51)
Study duration (years)			
Mean (SD)	0.92 (0.24)	0.92 (0.28)	0.92 (0.26)
Median	1.0	1.0	1.0
Min - max	0-1.1	0-1.1	0-1.1
Treatment duration (years)			
Mean (SD)	0.9 (0.26)	0.9 (0.28)	0.9 (0.27)
Median	1.0	1.0	1.0
Min - max	0-1.0	0-1.0	0-1.0
Number of doses			
Mean (SD)	25.2 (8.3)	45.8 (14.6)	35.7 (15.7)
Median	26.0	51.5	35.0
Min - max	1-37	2-52	1-52

Study duration (Years) = (date of last safety assessment – date of first study medication dose + 1)/365.25
Treatment duration (Years) =
(date of last study medication dose – date of first study medication dose + 8)/365.25 for pts on QW
(date of last study medication dose – date of first study medication dose + 11)/365.25 for pts on Q10D
(date of last study medication dose – date of first study medication dose + 15)/365.26 for pts on Q2W
Source: WA28118 Final CSR, Table 8, dated December 2017, page 69.

For this submission and this review, the safety data are compared to the data from the IV TCZ study WA18221 and from the LTE study WA29231. The maximum treatment duration for study WA29231 (through the cut-off date) was 2.9 years, and the maximum treatment duration for study WA18221 (through the LTE cutoff of May 2010) was 2.00 years. These both exceeded the maximum treatment duration in study WA28118, which was 1.0 year. The mean and median treatment duration for the All TCZ group in study WA 29231 was 1.36 and 0.77 years, respectively. The mean and median treatment duration for the All TCZ group in study WA18221 (through the LTE cutoff) was 1.18 and 1.14 years, respectively. The AE rate per 100 PY is the value calculated for each of these studies and is the value used for comparison. This calculation required the use of the total study duration sum, which was 46.74 PY in study WA28118, 50.25 PY in study WA29231, and 132.40 PY in study WA18221.

Relevant characteristics of the safety population:

The safety population was the same as the population evaluated for exploratory efficacy, and their characterized have already been described above. See Table 10 and Table 11.

The baseline demographics and patient characteristics were generally similar to the safety populations in the LTE study WA29231 and the IV TCZ study WA18221.

Adequacy of the safety database:

The entire enrolled population for study WA28118 comprised the population analyzed for PK, safety, and efficacy. The enrolled population was equality represented by both weight groups (<30 kg and ≥30 kg). Although age of onset is typically between 2 to 5 years-old, sJIA patients can be any age up to age 16. The majority of patients are Caucasian, like this patient population. African-American/black patients tend to have more severe disease. Only 1 subject (<30 kg) in study WA28118 was black.

10.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no important issues regarding data quality or the quality of the overall submission that had an effect on the safety review. No OSI audits were necessary.

Categorization of Adverse Events

The applicant utilized standard definitions of adverse events (AEs) and serious adverse events (SAEs).

The AEs of special interest (AESIs) were selected based on the underlying disease (sJIA) and the known risk profile of tocilizumab. The following are the AESIs and how the applicant defined them from the safety database.

- Serious infections (Infections and Infestations SOC filtered for serious)
- Opportunistic infections (Roche Standard Adverse Event Group Terms [AEGT] Opportunistic Infections)
- Hypersensitivity Reactions (AEs [excluding ISRs] during or within 24 hours of TCZ treatment and not unrelated to study medication)
- Anaphylactic reactions (Roche Standard AEGT Basket according to Sampson's criteria and Anaphylactic Reaction SMQ narrow)
- Injection Site Reactions (including all AEs with a preferred term [PT] under the "Injection Site Reactions" high-level term [HLT] or which had a "yes" response on the AE eCRF page to the question, "Did the event occur at injection site?")
- Serious Hepatic Events (Hepatic Failure, Fibrosis and Cirrhosis and Other Liver Damage-Related Conditions SMQ wide + Hepatitis, Non-infectious SMQ wide)
- Gastrointestinal Perforations (Gastrointestinal Perforations SMQ narrow)
- Demyelinating Disorders (Demyelination SMQ narrow)
- Myocardial infraction (MI)/acute coronary syndrome (MI SMQ narrow)
- Stroke (Hemorrhagic Cerebrovascular Conditions SMQ narrow + Ischemic Cerebrovascular Conditions SMQ narrow)
- Serious bleeding (Hemorrhage Terms [excluding lab terms] SMQ wide filtered for serious)

- Malignancies (Malignant Tumors SMQ narrow + Tumors of Unspecified Malignancy SMQ narrow)

Selected AEs were those selected for analysis but were not part of the protocol-defined expedited reporting requirements.

- Infection (Infections and Infestations SOC)
- Neutropenia (Roche standard AEGT for neutropenia)
- Thrombocytopenia (thrombocytopenia SMQ wide)
- Macrophage activation syndrome (low level term captured under the PT histiocytosis hematophagic)

The applicant presented all safety data by baseline BW, TCZ status, and an "All TCZ" category. A rate of AEs per 100 patient years was presented by preferred term and was based on the sum of the duration in study across all patients in the BW group.

Routine Clinical Tests

Laboratory samples (blood and urine) were collected according to the Schedule of Assessments outlined in the applicant's protocol for WA28118. The samples were measured for a number of laboratory parameters including basic hematology, blood chemistry, urinalysis, screening tests (hepatitis B surface antigen, hepatitis C antibody, HbA1c, EBV titer), acute phase reactants, lipid profile, PK/PD assessments, and immunogenicity assessments.

All laboratory data were reported in terms of standard pediatric normal ranges in System International (SI) units. Table 15 displays the CTCAE grading for abnormalities in hematology and liver enzymes parameters. For lipid parameters, elevation is categorized according to criteria identified specifically for childhood lipid screening: ≥200 mg/dL for total cholesterol (fasted) and ≥ 130 mg/dL for LDL cholesterol (fasted).

Table 15: NCI CTCAE Version 4.0 Grading for Hematology and Liver Enzymes Laboratory Abnormalities

	CTCAE Grade			
	1	2	3	4
Depression				
Neutrophils	1.5 x10^9/L to <LLN	1.0 x10^9/L to <1.5 x10^9/L	0.5 x10^9/L to <1.0 x10^9/L	<0.5 x10^9/L
Platelets	75 x10^9/L to <LLN	50 x10^9/L to <75 x10^9/L	25 x10^9/L to <50 x10^9/L	<25 x10^9/L
Elevation				
ALT	>ULN to 3.0x ULN [a]	>3.0 to 5.0x ULN [a]	>5.0 to 20.0x ULN	>20.0x ULN
AST	>ULN to 3.0x ULN [a]	>3.0 to 5.0x ULN [a]	>5.0 to 20.0x ULN	>20.0x ULN
Total bilirubin	>ULN to 1.5x ULN	>1.5 to 3.0x ULN	>3 to 10.0x ULN	>10.0x ULN

Source: BLA 125472/031 Summary of Clinical Safety, Table 5, submitted March 2018, page 26.

10.4. Safety Results

Overview of Safety

Table 16 summarizes the incidence and rate (per 100 PY) of the major categories of adverse events (all AEs, SAEs, AEs leading to death, AEs leading to discontinuation, and AEs leading to dose interruption) for the PK bridging study WA28118, the LTE study WA 29231, and the IV TCZ sJIA study WA18221.

Nearly all subjects in the SC study WA28118 experienced an AE, and this was similar to the experience with IV TCZ. The rate though appeared higher in study WA28118 for the All TCZ population (1200.3 per 100 PY in WA 28118 vs. 858.8 per 100 PY in WA18221) likely because of the shorter exposure. In general, the incidence of AEs in the major categories in study WA28118 (except for deaths) was similar to the IV study that led to original approval for sJIA.

Each of these key adverse events will be reviewed in further detail below.

Table 16: Overview of Safety in sJIA in Studies WA28118, WA29231, and WA18221 (Incidence and AE Rate)

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Data cutoff Aug 2017)			Study WA18221 (LTE cutoff May 2010)		
	162mg Q10D or Q2W (< 30 kg) (N=25)	162mg QW (≥ 30 kg) (N=26)	All TCZ (N=51)	162mg Q10D or Q2W (< 30 kg) (N=18)	162mg QW (≥ 30 kg) (N=19)	All TCZ (N=37)	12 mg/kg Q2W (< 30 kg) (N=50)	8 mg/kg Q2W (≥ 30 kg) (N=52)	All TCZ (N=112)[a]
Study Duration(PY)	22.95	23.79	46.74	14.73	35.52	50.25	57.18	63.81	132.40
AE	25 (100%)	25 (96.2%)	50 (98.0%)	10 (55.6%)	17 (89.5%)	27 (73.0%)	49 (98.0%)	51 (98.1%)	110 (98.2%)
No. of AEs	233	328	561	83	170	253	559	489	1137
Rate per 100 PY	1015.3	1378.7	1200.3	563.5	478.6	503.5	977.7	766.3	858.8
(95% CI)	(889.1, 1154.3)	(1233.4, 1536.3)	(1103.0, 1303.8)	(448.8, 698.5)	(409.4, 556.2)	(443.3, 569.5)	(898.3, 1062.2)	(699.9, 837.4)	(809.6, 910.2)
SAE	5 (20.0%)	2 (7.7%)	7 (13.7%)	1 (5.6%)	1 (5.3%)	2 (5.4%)	14 (28.0%)	9 (17.3%)	25 (22.3%)
No. of SAEs	7	2	9	1	1	2	17	13	33
Rate per 100 PY	30.5	8.4	19.3	6.8	2.8	4.0	29.7	20.4	24.9
(95% CI)	(12.3, 62.8)	(1.0, 30.4)	(8.8, 36.6)	(0.2, 27.8)	(0.1, 15.7)	(0.5, 14.4)	(17.3, 47.6)	(10.9, 34.8)	(17.2, 35.0)
AE with fatal outcome	2 (8.0%)	0	2 (3.9%)	0	0	0	0	0	1 (<1%)[b]
AE leading to withdrawal	1 (4.0%)	1 (3.8%)	2 (3.9%)	0	0	0	2 (4.0%)	2 (3.8%)	4 (3.6%)
No. of AEs	3	1	4				2	2	4
Rate per 100 PY	13.1	4.2	8.6	0	0	0	3.5	3.1	3.0
(95% CI)	(2.7, 38.2)	(0.2, 23.4)	(2.3, 21.9)				(0.4, 12.6)	(0.4, 11.3)	(0.8, 7.7)
AE leading to dose interruption	7 (28.0%)	6 (23.1%)	13 (25.5%)	3 (16.7%)	4 (21.1%)	7 (18.9%)	24 (48.0%)	28 (53.8%)	57 (50.9%)
No. of AEs	18	10	28	5	10	15	66	79	164
Rate per 100 PY	78.4	42.0	59.9	33.9	28.2	29.9	115.4	123.8	123.9
(95% CI)	(46.5, 124.0)	(20.2, 77.3)	(39.8, 86.6)	(11.0, 79.2)	(13.5, 51.8)	(16.7, 49.2)	(89.3, 146.9)	(98.0, 154.3)	(105.6, 144.3)

a The "All TCZ IV" group includes all patients in the WA18221 safety population, including those in dose groups not show
b The only fatal AE noted in the WA18221 LTE was in the switcher group (i.e., TCZ 12 mg/kg to 8 mg/kg because of change in weight)
Incidence = total number of patients with at least one of the AEs; Source: BLA 125472/031 Summary of Clinical Efficacy, submitted March 2018, page 11.

Deaths

Two deaths occurred in study WA28118. Both subjects were in the <30 kg group.

- Subject (b) (6) was an 8-year-old boy, TCZ naïve, who died from a pulmonary hemorrhage on Day 15. The subject only received 1 dose of 162mg TCZ SC on Day 1. Other concomitant medications included NSAIDs and prednisone for his sJIA. He developed nasal congestion on Day 12, cough and vomiting with blood on Day 13, and dyspnea on Day 14. On Day 15, he was diagnosed with oral candidiasis (SAE, Grade 2) and pneumonia (SAE, Grade 4). He was hospitalized and intubated. During the intubation, he experienced pulmonary hemorrhage followed by respiratory failure and a heart attack. Attempts at resuscitation failed. His cause of death was officially attributed to pulmonary hemorrhage. The investigator considered all SAEs (oral candidiasis, pneumonia, and pulmonary hemorrhage) attributable to study drug.

- Subject (b) (6) was a 13-year-old girl, TCZ naïve, who died from sepsis on Day 262. She was initiated on the Q2W dosing regimen and switched to QW dosing regimen on Day 218 after an increase in weight to ≥30 kg. She was also receiving concomitant MTX, folic acid, naproxen, and prednisone for her sJIA. Other medications included vitamin D and calcium. Prior to her death, she received a total of 20 TCZ SC doses with her last dose administered on Day 239. On Day 260, she was hospitalized with fever, ecchymoses, and neurological deterioration. She was diagnosed with sepsis from an unknown source. On Day 262, she died, and her death was attributed to sepsis and multi-organ failure. Another AE experienced by the subject during the course of the study was a non-serious Grade 1 AE of tooth abscess on Day 42. The investigator considered the SAE of sepsis as related to study drug.

Reviewer's Comment: It is notable that only 1 death occurred in the IV TCZ study in sJIA. However, the causes of the 2 deaths in this study can be attributed to infection (sepsis) and pulmonary hemorrhage in the setting of infection (pneumonia and oral candidiasis). Infection is a known risk of therapy in this patient population, and both subjects were taking multiple immunosuppressants including steroids.

Serious Adverse Events

In study WA28118, a total of 7 subjects experienced 9 SAEs. The majority occurred in the Infection and Infestations SOC (7.8% in the All TCZ group, 4 subjects with 5 SAEs). However, 3 of these SAEs in the Infection and Infestations SOC were already described above as causes of the 2 deaths in the study. Table 17 describes the subject narratives involving the SAEs. Other than infections, other SAEs included JIA flare (n=2) and vertigo (n=1). The SAE rate was calculated to be 19.3 events per 100 PY and was comparable to the rate in the IV TCZ study (WA18221).

Table 17: SAE Narratives (WA28118)

Subject ID TCZ Status Age/Sex TCZ Dose	Serious Adverse Event
<30 kg BW group: total 5 subjects with 7 SAEs	
(b) (6) Prior TCZ 17-month old boy Dose: Q10D	• On Day 310, the subject developed a hematoma (Grade 1, non-serious) and joint swelling (right knee). He was hospitalized and diagnosed with a soft tissue abscess in the right knee (Grade 3 SAE) on Day 329. The subject received oral and IV antibiotics and discharged on Day 330. The SAE was considered resolved on Day 336. The SAE was considered unrelated to study treatment. One dose of TCZ was missed due to the SAE. • The subject also had a Grade 2 neutropenia (1.2 x 10^9/L) on Day 341.
(b) (6) TCZ naïve 13 year-old girl Dose: Q2W → QW	Grade 5 SAE (fatal) of sepsis – described above
(b) (6) TCZ naïve 8 year-old boy Dose: Q2W	Grade 2 SAE of oral candidiasis, Grade 4 SAE of pneumonia, Grade 5 (fatal) SAE of pulmonary hemorrhage – described above
(b) (6) TCZ naïve 5 year-old boy Dose: Q2W	On Day 71, the subject presented with neck pain/rigidity along with left knee pain/swelling. He was diagnosed with reactivation of JIA (Grade 3 SAE). The SAE was considered resolved on Day 99. The investigator considered this SAE to be unrelated to study treatment. The subject remained in the study.
(b) (6) Prior TCZ 8 year-old boy Dose: Q2W	The subject developed cough on Day 53 and fever on Day 54. A CXR confirmed RLL pneumonia (Grade 3 SAE) on Day 54. He was hospitalized and treated with oral and IV antibiotics. On Day 64, he was discharged after the SAE resolved. TCZ treatment was interrupted because of the SAE. The investigator considered the SAE to be unrelated to study treatment.
≥ 30 kg group: 2 patients with 3 SAEs	
(b) (6) Prior TCZ 14 year-old boy Dose: QW	The subject received a TCZ dose on Day 8 and experience a sJIA flare on the same day (Grade 3 SAE). The subject was hospitalized on Day 10 to receive additional treatment. TCZ was discontinued, and the subject withdrew due to "lack of efficacy." The sJIA was unresolved at the time of last report, and the investigator considered the SAE to be related to study treatment.
(b) (6) TCZ naïve 16 year-old girl Dose: QW	The subject developed worsening vertigo on Day 259, attributed to hypertension. The subject was treated with acetyl leucine with improvement, and she was discharged. Vertigo was resolved by Day 351. TCZ treatment continued. The SAE was not considered related to study drug.

Source: WA28118 Final CSR, dated December 2017, page 78.

Dropouts and/or Discontinuations Due to Adverse Effects

Excluding death, there was only 1 subject who discontinued from the study due to an AE of sJIA flare or "lack of efficacy." This subject (b) (6)) was described above.

The applicant included 1 of the cases of death in their overall rate of AEs leading to study discontinuation, which was 8.6 per 100 PY. This was slightly higher than the rate (3.0 per 100 PY) in the IV study, but it is unclear if death was counted toward the rate in study WA18221. On the other hand, there was 1 subject (≥30 kg BW group) who was classified as withdrawing to due physician decision, but the physician made this decision due to persistently low neutrophil counts.

Low neutrophil counts was the most common cause for drug dose modification or interruption. In the All TCZ group, 13 subjects (25.5%) experienced 28 AEs that led to a modification or interruption in the dose. The rate of AE was 59.9 per 100 PY. This was lower than the rate in study WA18221 (123.9 per 100 PY).

Reviewer's Comment: In general, as with the causes of death and SAEs, the types of AEs leading to discontinuation were consistent with the experience from the IV study for sJIA. The overall numbers were small in this study.

Treatment Emergent Adverse Events and Adverse Reactions

In study WA28118, nearly all subjects in both BW groups experienced an AE. The most common AEs in study WA28118 overall were viral upper respiratory tract infection (25.5%), neutropenia (25.5%), cough (23.5%), upper respiratory tract infection (21.6%), injection site erythema (19.6%), vomiting (17.6%), rash (15.7%), diarrhea (13.7%), and rhinitis, injection site pain, oropharyngeal pain, abdominal pain, leukopenia, headache, and injection site pruritus (all 11.8%). These were generally consistent with the most common AEs in study WA18221, which were upper respiratory tract infection, headache, nasopharyngitis, and diarrhea.

The frequency of some adverse events appeared to differ based on baseline BW group, dose frequency (in the <30kg BW group), and TCZ status.

- Baseline BW group
  - The SOC of Infections and Infestations occurred in 88% of subjects in <30 kg BW group vs. 69.2% in the ≥30 kg group.
  - The SOC General Disorders and Administration Site Conditions was more frequent in the ≥30 kg group at 69.2% vs. 36.0% in the <30 kg group.
- Dosing frequency in <30 kg group
  - A difference was noted in the Injury, poisoning, and procedural complications SOC and the Respiratory, thoracic, and mediastinal disorders SOC, where more subjects receiving the Q2W experienced AEs compared to the Q10D subjects.
  - On the other hand, more subjects on the Q10D dosing regimen experienced AEs

in the General disorders and administration site conditions SOC compared with subjects on the Q2W regimen.

- TCZ status
  - More TCZ naïve subjects (57.7%) experienced AEs in the Respiratory, thoracic, and mediastinal disorders SOC compared to the Prior TCZ subjects (40.0%).
  - More subjects who had Prior TCZ experience (64.0%) reported AEs in the General disorders and administration site conditions compared to TCZ naïve subjects (42.3%).

Laboratory Findings

There are known risks with the use of TCZ on certain laboratory parameters. These are highlighted here.

Neutropenia

Of 51 subjects in study WA28118, 48 subjects had a normal baseline neutrophil, and 23 had a normal post-baseline neutrophil count. Post-baseline, 3 (5.9%) had a Grade 1 low neutrophil count; 13 (25.5%) Grade 2 low neutrophil count; and 12 (23.5%) Grade 3 low neutrophil count. The proportion of patients with low neutrophil count abnormalities and Grade 3 neutropenia was lower in the <30 kg BW group. Six of the 12 subjects with Grade 3 neutropenia had this level of neutropenia at a single time point. Of the 4 subjects who experienced the 5 serious infections in this study, only 1 (with the soft tissue abscess) had a low neutrophil count within 15 days of the event.

Additionally, 13 subjects in the All TCZ group (representing subjects with both BW and both TCZ status) had 33 neutropenia AEs. None were serious. No serious infections were associated with a neutropenia event.

The rate of neutropenia per 100 PY was calculated to be 70.6 in the All TCZ group. There was a slightly higher rate in the <30 kg group (91.5 per 100 PY in <30 kg vs. 50.4 per 100 PY in the ≥30 kg). The rate was also slightly higher for the Q2W regimen compared to the Q10D regimen in the <30 kg group, 70.3 per 100 PY and 101.0 per 100 PY, respectively. These rates were slightly higher than what was seen in the IV TCZ study where the rate of neutropenia in the All TCZ group was 43.8 per 100 PY. In the LTE study, the rates decreased.

Thrombocytopenia

Forty-nine subjects had normal baseline platelet counts, and the majority (74.5%) maintained platelet counts within normal range post-baseline. Twelve subjects (23.5%, 10 subjects in <30 kg group [9 on Q2W] and 2 subjects in the ≥30 kg group) developed a Grade 1 low platelet count. No subjects developed a Grade 2, 3, or 4 low platelet count.

Two subjects experienced a bleeding event (19-month old girl with a non-serious contusion and a 7-year-old boy with non-serious epistaxis) within 15 days of a low platelet count. The subject

with the fatal bleeding event had normal platelet counts.

Additionally, 2 subjects weighing < 30 kg had an AE of thrombocytopenia. Both were non-serious, and only 1 led to drug interruption. Both events resolved. No bleeding event occurred within 15 days of these thrombocytopenia AEs. The rate of thrombocytopenia AEs for the All TCZ group was 4.3 per 100 PY. The rate was maintained and even lower in the LTE. The rate was comparable to that in study WA18221.

Macrophage Activation Syndrome (MAS)
No events of MAS occurred in this study, nor in the LTE. Three subjects in the IV study did experience MAS.

Elevated liver enzymes
Of the 50 subjects who had a normal ALT at baseline, 12 (24.0%) developed a post-baseline Grade 1 elevation; 3 (6.0%) Grade 2 elevation; 1 (2.0%) Grade 3 elevation. The Grade 3 post-baseline elevation was recorded at a single time point. One subject started with a Grade 3 elevation at baseline and then had a Grade 4 elevation post-baseline. This elevation persisted for 13 days and then decreased to a Grade 1 elevation with continued TCZ. This subject had a history of concomitant indomethacin use.

Of the 48 subjects who had a normal AST at baseline, the majority (38/48, 79.2%) maintained a normal AST post-baseline. Nine subjects (18.8%) had post-baseline Grade 1 elevation, and 1 subject had a Grade 2 elevation. One patient had a Grade 2 elevation at baseline, which increased to Grade 3 post-baseline. This is the same subject who was utilizing indomethacin described above. No Grade 4 elevations occurred.

Of the 39 subjects with a normal total bilirubin at baseline, 33 maintained a normal total bilirubin level. Four subjects (10.3%) had a post-baseline Grade 1 elevation, and 2 subjects had a Grade 2 elevation. There were no Grade 3 or 4 elevations in bilirubin.

Five subjects had an elevation in ALT ≥ 3x ULN, and 2 subjects had an elevation in AST ≥ 3x ULN. No subjects met laboratory criteria for Hy's law. Additionally, there were no hepatic AEs (serious or nonserious) during this study.

Lipid panel
In the All TCZ group, 16 subjects (33.3%) experienced an elevation in total cholesterol ≥ 200 mg/dL, and 11 subjects (23.4%) experienced an elevation LDL ≥ 130 mg/dL. These occurred in generally similar proportion for the two BW groups. Additionally, for the majority of these lipid elevations, they were measured at a single time point.

Vital Signs and Other Tests

The majority of subjects had vital signs (blood pressure and heart rate) that remained within

the normal range. There was a question whether 2 subjects in the ≥30 kg group may have had a BW loss of >10% from baseline, but the applicant reported that this finding was due to a measurement error.

The applicant also reports that 1 subject (17 year-old girl, >30 kg) had an abnormal chest x-ray at baseline. No chest x-rays needed to be done for a positive PPD during the study.

Immunogenicity

Anti-TCZ antibodies were measured for all subjects at approximately 3-month intervals during the study and at the last study visit. The protocol also allowed for event-driven sampling for any subjects who experienced a serious injection-related or allergic reactions or hypersensitivity reactions leading to withdrawal.

As already described in Clinical Pharmacology Section 6.2.2, all 51 subjects had a screening assay result at baseline, and 46 subjects had at least 1 post-baseline screening assay result. Three subjects (5.9%) tested screening assay positive at positive, but all subjects, including these 3, were ADA negative post-baseline. Of note, 1 of the baseline positive subjects had a history of prior TCZ experience. Thus, no analysis of efficacy or safety based on anti-drug antibodies (ADA) was performed.

Similarly, in the LTE study WA28231, all subjects (n=37, 100%) were evaluated at baseline, and 26 subjects (70.3%) had at least 1 post-baseline screening assay. None of these subjects were screening assay positive (both baseline and post-baseline).

Immunogenicity in study WA18221 was reviewed with BLA 125276/S-022.

10.5. Analysis of Submission-Specific Safety Issues

The AEs of special interest (AESIs) were selected based on the underlying disease (sJIA) and the known risk profile of tocilizumab. The AESIs and Selected AEs were already identified defined in Section 10.3. Table 18 displays all the AESIs and Selected AEs for studies WA28118, the LTE WA29231, and the IV study WA18221. These AEs will be reviewed in more detail below.

Table 18: Incidence of AESIs and Selected AEs in sJIA in Studies WA28118, WA29231, and WA18221

	TCZ SC						TCZ IV		
	Study WA28118 (Week 52)			Study WA29231 (Data cutoff Aug 2017)			Study WA18221 (LTE cutoff May 2010)		
	162mg Q10D or Q2W (< 30 kg) (N=25) n (%)	162mg QW (≥ 30 kg) (N=26) n (%)	All TCZ (N=51) n (%)	162mg Q10D or Q2W (< 30 kg) (N=18) n (%)	162mg QW (≥ 30 kg) (N=19) n (%)	All TCZ (N=37) n (%)	12 mg/kg Q2W (< 30 kg) (N=50) n (%)	8 mg/kg Q2W (≥ 30 kg) (N=52) n (%)	All TCZ (N=112)[a] n (%)
Infections	22 (88.0%)	18 (69.2%)	40 (78.4%)	9 (50.0%)	13 (68.4%)	22 (59.5%)	43 (86.0%)	44 (84.6%)	97 (86.6%)
Serious infections	4 (16.0%)	0	4 (7.8%)	1 (5.6%)	0	1 (2.7%)	9 (18.0%)	5 (9.6%)	15 (13.4%)
Opportunistic infections	0	0	0	0	0	0	N/A[b]	N/A[b]	N/A[b]
Hypersensitivity reactions	2 (8.0%)	1 (3.8%)	3 (5.9%)	0	0	0	14 (28.0%)	10 (19.2%)	25 (22.3%)
Anaphylactic reactions	0	0	0	0	0	0	1 (2.0%)	1 (1.9%)	2 (1.8%)
Injection site reactions	5 (20.0%)	16 (61.5%)	21 (41.2%)	0	3 (15.8%)	3 (8.1%)	N/A	N/A	N/A
Serious bleeding AEs	1 (4.0%)	0	1 (2.0%)	0	0	0	0	0	0
Neutropenia	5 (20.0%)	8 (30.8%)	13 (25.5%)	2 (11.1%)	3 (15.8%)	5 (13.5%)	11 (22.0%)	8 (15.4%)	20 (17.9%)
Thrombocytopenia	2 (8.0%)	0	2 (3.9%)	0	1 (5.3%)	1 (2.7%)	2 (4.0%)	2 (3.8%)	4 (3.6%)
MAS	0	0	0	0	0	0	1 (2.0%)	1 (1.9%)	3 (2.7%)

Incidence = Total number of patients with at least one of the AEs
a The "All TCZ IV" group includes all patients in the WA18221 safety population, including those in dose groups not show
b MedDRA basket for Opportunistic Infections not available for MedDRA Version 13
Source: BLA 125472/031 Summary of Clinical Efficacy, submitted March 2018, page 11

Infections

General infections
Most subjects in study WA28118 had at least 1 AE in the Infection and Infestation SOC. A higher proportion of subjects < 30 kg (88.0%) reported an infection AE compared with subjects ≥ 30 kg (69.2%). The proportion of subjects with an infection AE was similar by TCZ status (80.8% of TCZ naïve and 76.0% of Prior TCZ).

The most common infection AEs were viral upper respiratory tract infection (25.5%), upper respiratory tract infection (21.6%), and rhinitis (11.8%).

The rate of general infection in study WA28118 was 258.9 per 100 PY. The rate was slightly higher in the lower weight group (331.2 per 100 PY in <30kg group vs. 189.2 per 100 PY in ≥30 kg group). These rates did not increase with time, and, in fact, rates were lower in the LTE. These rates were actually similar to the IV TCZ study in sJIA. The rate of infection in the <30 kg group was 374.3 per 100 PY vs. 200.6 per 100 PY in the ≥30 kg group vs. 280.2 per all TCZ group.

Serious infections
In study WA28118, there were 5 serious infections reported by 4 subjects (all <30 kg). The serious infections were already described in the SAE narratives and included pneumonia (2 events), soft tissue abscess, oral candidiasis, and sepsis. These serious infections occurred in subjects on the Q10D dose (soft tissue abscess), Q2W dose (oral candidiasis, 2 cases of pneumonia), and QW (sepsis). One of the cases of pneumonia and the case of soft tissue abscess resolved. The other serious infections were involved in the 2 deaths that occurred in the study.

The rate of serious infections in study WA28118 was 10.7 per 100 PY. This rate did not increase with time (in the LTE study). It is also comparable to rate in the IV TCZ study WA18221, 11.3 per 100 PY.

Opportunistic infections
No opportunistic infections occurred in this study and were not reported in the supportive studies either. No subjects had a positive PPD.

Hypersensitivity Reactions

A total of 3 subjects in study WA28118 experienced 4 potential hypersensitivity reactions. These reactions were hypersensitivity (PT), decreased platelet count, pruritus, and pyrexia. The rate for all TCZ subjects was calculated at 8.6 per 100 PY. This was much lower than the rate for IV TCZ, 30.2 per 100 PY. The sponsor does note that there was one subject in study WA28118 who is recorded as having an injection site reaction (ISR), but his ISR may be better categorized

as a hypersensitivity reaction because he had mild systemic symptoms (headache, vertigo, fatigue.

No subjects experienced anaphylaxis defined by either the anaphylactic reaction SMQ narrow or Sampson's criteria.

Injection Site Reactions

Twenty-one subjects (41.2%) were documented as having at least 1 injection site reaction (ISR), specifically a total of 136 ISRs. A smaller proportion of the <30 kg group (20.0%) compared to the ≥ 30 kg group (61.5%) had an ISR. Most of the ISRs in the ≥ 30 kg group could be attributed to 4 female subjects who reported 90 of the 122 ISRs in that category. Overall, the most commonly reported ISRs were injection site erythema, injection site pain, injection site pruritus, injection site reaction, and injection site swelling. The documented ISRs were non-serious and did not require treatment withdrawal or even dose interruption.

The rate of ISRs per 100 PY was calculated to be 291.0 per 100 PY. ISRs continued to occur in the LTE study at a lower rate. There was a total of 3 ISRs in the LTE study. ISRs are not applicable for the IV TCZ study in sJIA. Instead, the applicant provides the rate of ISRs per 100 PY in the SC TCZ for pJIA study (WA28117). For the All TCZ group, the rate was 113.0 per 100 PY, thus slightly smaller than the rate in the sJIA study. Notably, the rates of ISRs in pediatric diagnoses (sJIA and pJIA) were higher than what was calculated for the adult RA studies, 30.1-33.6 per 100 PYs.

Serious Bleeding Events

One subject ((b) (6)) experienced an SAE of pulmonary hemorrhage, already described above. Based on this 1 event, the rate of serious bleeding AE per 100 PY was 2.1 in the All TCZ group.

Other AESIs and Selected AEs for Analyses

The other AESIs of GI perforations, demyelinating disorders, myocardial infarction, stroke, and malignancies did not occur in study WA28118.

Neutropenia, thrombocytopenia, and MAS were designated "selected AEs for analyses," but they are described under Laboratory Findings in Section 10.4.

10.6. Safety Analyses by Demographic Subgroups

The safety of the different body weight groups and TCZ status are discussed in the above review of safety.

The applicant also evaluated the rate of overall AEs in the <30 kg body weight based on dosing regimen (Q10D and Q2W). The rate of overall AEs was similar: 984.5 per 100 PY (95% CI: 767.5, 1243.9) for those who received Q10D and 1029.0 per 100 PY (95% CI: 877.1, 1199.7) for those who received Q2W.

Lastly, the applicant provided safety information in the 3 subjects who were < 2 years and the 1 subjects who weighed <10 kg at baseline. Table 19 presents details of the safety experience of these subjects. There was only 1 SAE of a soft tissue abscess that resolved. The AEs of these subjects were consistent with subjects ≥ 2 years of age.

Table 19: Safety Overview of sJIA Patients < 2 Years and Lightest Weight (WA28118)

Subject ID Country (# of AEs)	Age and Sex	BW	TCZ Status	TCZ SC Dose	SAE(s)	Grade 3 AEs or Grade 3 Laboratory abnormalities (Neutrophils, platelets, LFTs)
< 2 years old						
(b) (6) Germany (Total 22 AEs)	17 months, male	10.3 kg	Prior TCZ	Q10D	Abscess soft tissue SAE on D329 • Resolved after 8 days • Dose interrupted • Considered unrelated by investigator	• Grade 3 abscess (same as SAE) • Grade 3 low neutrophil counts D30: 0.9 x 10^9/L D371: 1.0 x 10^9/L
(b) (6) Spain (Total 17 AEs)	19 months, female	11.0 kg	Prior TCZ	Q2W	None	Grade 3 neutropenia AE on D69 • Resolved after 16 days • No dose change • Considered unrelated by investigator
(b) (6) USA (Total 15 AEs)	22 months, female	11.5 kg	Prior TCZ	Q2W	None	No Grade 3 AEs Grade 3 elevated ALT D154: 172 (U/L)
< 10 kg BW at baseline						
(b) (6) Spain (Total 4 AEs)	25 months, female				None	No Grade 3 AEs or lab abnormalities

Source: BLA 125472/031 Clinical Overview, Table 6, submitted March 2018, page 47.

10.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No information on human carcinogenicity or tumor development is included in this

supplement.

Human Reproduction and Pregnancy

No pregnancies have been reported in clinical studies with TCZ in sJIA patients. Adequate data relating to the use of TCZ in pregnant women are not available. It is also unknown whether TCZ was excreted in human breast milk.

Nonclinical data of IV TCZ and pregnancy and lactation were evaluated with previous submissions.

Pediatrics and Assessment of Effects on Growth

Height was measured by the applicant using the height standard deviation score (SDS). The height SDS was calculated as (observed height-median value of the reference population)/SD of the reference population. The reference population was defined by World Health Organization (WHO) norms for the same sex and age.

At baseline, the TCZ naïve subjects <30 kg had a mean height SDS below the normal reference range, but the height SDS increased at Month 6 and Year 1 towards the normal reference range. Mean height SDCs for the other subgroups (TCZ naïve subjects ≥30 kg group, Prior TCZ subjects both <30 kg and ≥30 kg) were close to normal reference range at baseline and remained stable to mildly increased over 12 months.

Thus, utilizing the height SDS and other height measurements such as the height velocity score, the applicant reports that SC TCZ led to an improvement in growth, consistent with that observed with IV TCZ in sJIA.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of TCZ overdose have been reported in clinical studies in sJIA. There have been cases of TCZ overdose in other indications (e.g., adult RA) without associated AEs.

There are no safety data on withdrawal or rebound in subjects with sJIA treated with SC TCZ.

10.8. Safety in the Post-Market Setting

The international birthdate (IBD) of TCZ is April 11, 2005, the date that TCZ was first granted marketing approval in Japan for the treatment of Castleman's disease. The US approvals of TCZ are summarized in Section 3.1. TCZ IV has been approved in over 100 countries worldwide, and TCZ SC has been approved in over 90 countries.

In the most recent Periodic Benefit-Risk Evaluation Report (PBRER, data lock point of April 10, 2017), the estimated cumulative total of (b) (4) patients ((b) (4) PY) have received TCZ from marketing experiences across all indications and regions. The estimated cumulative post-marketing exposure to TCZ for sJIA is (b) (4) patients ((b) (4) PY). Post-marketing safety data for the PBRER were obtained from non-interventional studies (e.g., post-authorization safety studies), reports from other solicited sources, and spontaneous individual case safety reports (e.g., reports from healthcare professionals, consumers, health authorities, and scientific literature). No new safety signals were identified.

10.9. Integrated Assessment of Safety

The objective of the safety data from this open-label, uncontrolled study is to support the PK bridge. Again, the conclusions from the safety analyses are, thus, limited. Importantly, most of the safety were consistent with what was reported with IV TCZ for the treatment of sJIA. Additionally, for the LTE study, there was no worsening in safety with longer exposure.

There were 2 deaths in study WA28118, which exceed what was reported in study WA18221 (the IV TCZ study in sJIA). The causes of death (namely, infection and pulmonary hemorrhage with underlying infection) were not unexpected.

Injection site reactions (ISRs) occurred in this study and is a new safety signal for sJIA because ISRs would not have been an issue in the IV study. The ISRs were consistent, however, with what was noted in the pJIA SC study. Notably, the rates of ISRs were slightly higher in the pediatric indications compared to adult RA.

Any comment on immunogenicity in this study is further limited because there were no post-baseline anti-drug antibodies.

Lastly, the sponsor again highlights the safety data from the 3 subjects who were less than 2 years-old. There was 1 SAE (soft tissue abscess) and 2 cases of Grade 3neutropenia, thus,

consistent with the safety from the rest of the study. It is difficult to make any conclusions for this safety population beyond the conclusions from the safety data as a whole and that is that the safety data from study WA28118 support the PK bridge.

SUMMARY AND CONCLUSIONS

11 Conclusions and Recommendations

Genentech submitted the PK and supportive clinical data from study WA28118 to support the treatment of sJIA with SC TCZ. The basis of regulatory action for this supplement is the PK bridge to the safety and efficacy of IV TCZ in patients with sJIA. The safety and efficacy data from Study WA28118 are supportive of the PK analyses.

Overall, the safety and efficacy data were consistent with the data from the IV TCZ study in sJIA. The clinical data support the PK bridge to the IV TCZ program, which is the treatment of patients 2 years and older with active systemic JIA. Thus, the recommendation from a clinical perspective is that SC TCZ be approved for the treatment of patients 2 years and older with active systemic JIA.

The data are insufficient to support (b) (4), as proposed by the applicant. (b) (4)

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Primary Clinical Reviewer Clinical Team Leader

12 Advisory Committee Meeting and Other External Consultations

An advisory committee (AC) meeting was not recommended for this supplemental BLA. The efficacy and safety data in this supplement are generally consistent with what was reported with the original approval of TCZ (IV) for sJIA. No issues were identified that would warrant AC discussion.

13 Pediatrics

This supplement and its supporting study (WA28118) fulfills Study 3 of the Pediatric Written Request, issued to Hoffman-La Roche, Inc. on November 15, 2012, and amended on June 27, 2017. Study WA28118 meets the study design, objective, patients to be studied, endpoints, and timeline as outlined for Study 3 of the Pediatric WR. Thus, this portion of the WR should be considered fulfilled. The supplement was also discussed at the FDA Pediatric Review Committee (PeRC) on July 25, 2018. PeRC agreed with division's assessment.

This is the one of the 4 studies of the WR to be fulfilled. Study 1 was fulfilled with the submission of BLA 125275/S-115 on November 10, 2017. Study 2 was fulfilled with the submission of the CSR for study WA19977 LTE through Week 104 on July 18, 2013, reviewed under a separate memo. Study 4 was fulfilled with the submission of BLA 125472/S-028 on November 14, 2017. Thus, with the submission of this supplement, the applicant has met the timeframe for completion of the Pediatric WR on or before September 30, 2020. The Pediatric WR and the applicant's submissions were reviewed by the Pediatric Exclusivity Board, and tocilizumab was granted pediatric exclusivity on July 18, 2018.

14 Labeling Recommendations

14.1. Prescription Drug Labeling

Table 20 provides a summary of labeling proposal and interactions between the applicant and the Agency. In brief, based on the data from study WA28118, the applicant proposes updating the US prescribing information (USPI) with the indication for treatment of sJIA with SC TCZ. The applicant also proposes (b) (4) .

Table 20: Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)	
Section	**Labeling Discussions**
1.4 Indications and Use, 2.4 Dosage and Administration, 8.4 Pediatric Use, Medication Guide	(b) (4)

	(b) (4) (b) (4) A revised indication was agreed on by the applicant on September 10, 2018.
2.4 Dosage and Administration	The Agency also recommended that the order of bullets be rearranged to be consistent with Section 2.3 (SC TCZ in pJIA). The applicant agreed to these changes.
6.7 Clinical Trials Experience in sJIA Treated with ACTEMRA-SC	As there were no qualitative or notable quantitative differences from the safety in IV TCZ for sJIA, except for Injection Site Reactions (ISRs) and immunogenicity, the Agency recommended only leaving those 2 AEs along with the statement that the safety observed for SC TCZ was consistent with the known safety of IV TCZ. The applicant agreed with these changes.
12.3 Pharmacokinetics	Under the sJIA section, the Agency recommended that the applicant use observed PK values instead of model-predicted PK values. In response, dated August 20, 2018, the applicant proposed that the observed data are similar to the model-predicted PK values. Additionally, the PK data for the other approved indications are model-predicted values, and, thus, utilizing model-predicted values would allow for consistency. The Agency found the applicant's rationale to be acceptable and agreed with keeping the model-predicted PK values.
14.7 Clinical Studies: sJIA – Subcutaneous Administration	The Agency recommended abbreviating the study information and utilizing similar language to that used for pJIA – SC administration. In general, a

	statement that efficacy is based on PK exposure and extrapolation of efficacy of the IV TCZ in sJIA would be sufficient. The applicant agreed with the Agency's recommendation.

Final agreement on the above labeling was reached on September 10, 2018.

15 Risk Evaluation and Mitigation Strategies (REMS)

Tocilizumab (ACTEMRA) was released from its REMS requirement (originally approved on January 8, 2010, and modified on October 21, 2013) on August 18, 2015, based on the confirmation that there has been at least 1 complete assessment; the REMS goals were met; and there were no identified or emerging safety issues that require continued or new communication within the subsequent 6 months.

No new risk management plants are submitted as part of this supplement, and no new REMS are necessary.

16 Postmarketing Requirements and Commitment

There are no potential or new safety or efficacy issues determined from this review that warrant further assessment with a postmarketing requirement (PMR) or postmarketing commitment (PMC).

17 Division Director (or designated signatory authority)

I agree with the team's recommendation for limiting the age group to ≥ 2 years of age.
I recommend approval.

18 Appendices

18.1. References

Minoia F, Davì S, Horne A, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol*. 2014; 66: 3160-3169.

Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004; 31: 390-392.

Ravelli A and Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007; 369 (9563): 767-78.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Arthritis Rheumatol*. 2016; 68: 566-576.

Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013; 65: 2499-2512.

Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. *Arthritis Rheum*. 2006; 54: 1595-1601.

18.2. Financial Disclosure

The applicant provides financial disclosure information for study WA28118, the primary study that supports this supplement. Studies WA18221 (IV TCZ in sJIA) and WA29231 (the LTE study of WA28117 and WA28118) are supportive studies. As part of this supplement, the applicant provides financial disclosure information for study WA29231. The financial disclosure information for study WA18221 was reviewed with the approval of BLA 125276 Supplement 022. The tables below provide the details of the financial disclosure information collected and tracked by the applicant.

The same 2 investigators at the same clinical site ([redacted] (b) (6) [redacted] (b) (4) [redacted]) disclosed positive financial disclosures for both

(b) (4). This clinical site recruited a total of (b) (6) patients for study (b) (4) and (b) (6) patient for study (b) (4). The applicant provided information regarding the nature of the financial arrangement and steps taken to minimize potential bias; this information is described in Section 8.1.2 (Study Results for (b) (4)). The same information applies for study (b) (4).

Covered Clinical Study (Name and/or Number): WA28118

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 197 (43 prinicipal investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study Sponsor(s): 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None, all investigators provided financial disclosure		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 29231 (ongoing LTE study)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 107 total (21 prinicipal investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study Sponsor(s): 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None, all investigators provided financial disclosure		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

18.3. OCP Appendices (Technical documents supporting OCP recommendations)

Office of Clinical Pharmacology: Pharmacometric review

Note: Any text in this review with a light background should be inferred as copied from the sponsor's document.

18.3.1. Results of Sponsor's Analysis

Population PK analysis

Analysis Dataset Collected in Study WA18221 and WA28118

The analysis dataset contained 878 PK samples from 89 patients of Study WA18221 and 832 PK samples from 51 patients of Study WA28118. A total of 1,710 samples from 140 patients were used in the analysis. See Table 21 for a summary of both studies.

Table 21: Summary of clinical studies to assess PK and PD of TCZ in patients with sJIA.

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

Source: Adjusted from Table 1 on Page 16 of summary-clin-pharm.pdf (\\cdsesub1\evsprod\bla125472\0164\m2\27-clin-sum\summary-clin-pharm.pdf)

Model Building

The summary of population PK model development is presented in Table 22. Modeling started from the two-compartment Model 001 which was the final model developed in the earlier population PK analysis of pJIA data.

The data from study WA28118 included several patients with higher than expected residual error. To mitigate the effect of observation-outliers, Model 010 added the inter-individual variability (IIV) to the residual error. Diagnostic plots and high relative standard errors (RSEs) of off-diagonal terms of the variance-covariate matrix indicated limited correlations between the random effects. Model 013 simplified the variance-covariate matrix, assuming perfect correlation (R=1) between the random effects on V_M and V_C and no other correlations.

Model 013 included the effect of HT on Vc and the effects of BSA on CL, V_P, and V_M. As it would be more convenient to have one body size measure responsible for scaling of all PK parameters, Model 016 replaced HT by BSA in dependence of V_C on body size. The power coefficients that described dependence of model parameters (CL, V_C, V_P, and V_M) on BSA were estimated to be very similar; therefore Model 017 assumed them to be equal. Similarly, the effects of SEX were similar for V_C and V_M (the effect on V_P was the same as on V_M), therefore Model 018 assumed the same dependence of CL, V_M, V_C, and V_P on SEX. This decreased the number of parameters by 1 and decreased the OFV. Model 020 that added the same effects of BSA and SEX on Q (without adding number of estimated parameters) further reduced OFV. Model 026 that allowed separate effects of BSA and SEX on CL and Q versus V_M, V_C, and V_P did not improve the fit.

Models 031 - 035 explored removing the effect of BMI (Model 031), adding the effect of injection sites (Models 034 - 035), or adding IIV (Model 032) to subcutaneous bioavailability Fsc. None of these models improved the fit. Model 022 that tested the effect of AGE instead of BMI as a covariate on ka, also did not improve the model. Model 027 attempted to add the effect of study on the residual error, but it was rejected.

Models 037-040 explored the possibility of population and/or individual values of subcutaneous bioavailability (F_{SC}) to exceed 1. While models with individual F_{SC} values exceeding 1 had lower objective function values, diagnostic plots were not improved and these models were rejected as not mechanistically plausible.

Thus, Model 020 was accepted as the final model of the analysis. It's parameter estimates are provided in Table 23.

Model Evaluation

The basic goodness-of-fit plots for the final Model 020 stratified by study (and thus, by route of administration) indicate the absence of systematic bias and the adequacy of the model. In addition, conditional weighted residuals and individual weighted residuals also show the random normal scatter around zero with no specific pattern.

There were no dependencies of the random effects on gender, body weight, body mass index, body surface area, height, age, serum creatinine, and creatinine clearance.

There were 2 patients in study WA18221 with detected treatment-emergent ADAs. No treatment-emergent ADAs were detected for patients in study WA28118. Due to the very limited number of patients who were ADA positive following TCZ SC and IV administration, the exposure ADA relationship cannot be fully assessed for the sJIA patient population.

The results of the predictive check evaluation (VPC and NPDE plots) indicated that the model correctly captured both the central tendency and the inter-individual variability of tocilizumab pharmacokinetics following IV and SC administration, as well as dependence of the tocilizumab PK parameters on covariates. Plots indicated some underestimation of concentrations following SC Q2W administration, but it is likely due to the small size of the data set that contained only 51 subjects with SC administration.

Predictive check simulations for C_{trough} concentrations at week 12 showed an adequate predictability for IV and SC dosing regimens (Figure 15). Median C_{trough} values at week 12 following SC dosing were under-predicted by 32% for WT < 30 kg on Q2W regimen and by 17% for WT > 30 kg; the values for WT < 30 kg on Q10D and for IV regimens were predicted well. Overall, the model provided an adequate description of the IV and SC data.

Table 22: Summary of NONMEM Runs for Model Development

Run	Description	OFV	Comment
001	Final model of pJIA analysis	11301.39	Initial
010	As 001 with ETA on EPS	11252.58	Accepted
013	As 010, with reduced correlation matrix	11256.74	Accepted
016	As 013 with BSA on V_C instead of HT	11251.44	Accepted
017	As 016 with same BSA effects on CL, V_C, V_P, V_M (two parameters removed)	11258.23	Accepted
018	As 017 with same SEX effect on CL, V_C, V_P, V_M (one less parameter)	11254.42	Accepted
020	As 018 with same effects of BSA and SEX on Q as for CL (no parameters added)	11218.79	Final Model
026	As 020, but BSA and SEX effects on CL and Q (same for them) differ from other parameters (2 additional estimated parameters)	11218.56	Rejected
031[a]	As 020 with no BMI effect on F_{sc}	11240.34	Rejected
032[b]	As 020 with ETA on F_{sc} ($F_{sc} \leq 1$)	11212.60	Rejected
034	As 020 with SINJ=2 effect on F_{sc}	11215.84	Rejected
035[c]	As 020 with SINJ=3 effect on F_{sc}	11216.04	Rejected
022	As 020 with AGE on k_a instead of BMI	11217.87	Same OFV
027[d]	As 020 with study effect on the residual error	11215.66	Rejected
038	As 020 with no restriction on F1 (can be > 1)	11221.88	Rejected
039	As 020 with no restriction on population value of F1 and random effect on F1 (with individual F1 allowed to be > 1)	11193.94	Similar fit. Not mechanistic.
140	As 020 with restriction on population value (F1<=1) and random effect on F1 (with individual F1 allowed to be > 1)	11193.08	

a. Terminated due to a rounding error and provided 2.6 significant digits.
b. Covariance step failed.
c. Terminated due to a rounding error; F_{SC} estimated at the upper bound 1; covariance step failed.
d. Terminated due to a rounding error, and provided 1.9 significant digits.

Source: Table 7 on Page 46 of 1084039.pdf

Table 23: Parameter Estimates for the Final Model 020

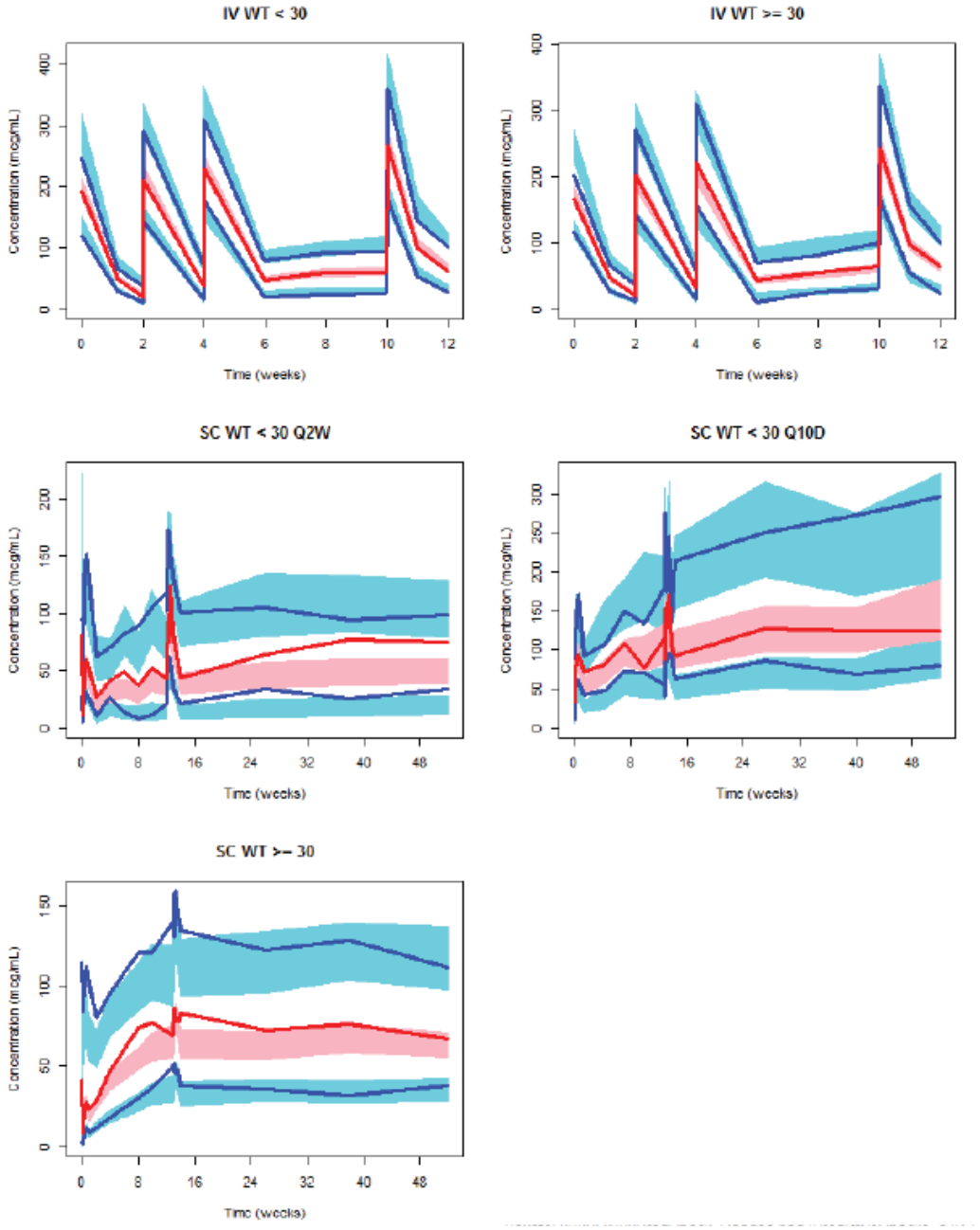
Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
CL (L/day)	θ_1	0.137	4.53	0.125 - 0.149		
V_C (L)	θ_2	1.87	3.24	1.75 - 1.99		
V_P (L)	θ_3	2.14	8.00	1.81 - 2.48		
V_M (mg/L/day)	θ_4	6.6	10.3	5.27 - 7.93		
Q (L/day)	θ_5	0.354	6.37	0.31 - 0.399		
K_M (µg/mL)	θ_6	4.61	36.8	1.28 - 7.94		
k_a (1/day)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

SE: Standard Error; RSE: Relative Standard Error, RSE=100·SE/PE;
95% CI: 95% confidence interval;
SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

Source: Table 8 on Page 47 of 1084039.pdf

Figure 15: Visual Predictive Check for Model 020, by Route of Administration, Weight Group, and Dosing Regimen

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



Source: Figure 36 on Page 101 of 1084039.pdf

Reviewer's comments: The covariate selection procedure has been implemented based on the established popPK model for TCZ in pJIA patients. Given the model building procedure

and the various model validation techniques used for the popPK model for TCZ in sJIA patients, the population PK model for TCZ in sJIA seems reasonable based on model diagnostics.

Predictive check results show under prediction for trough concentrations following SC administration (both Q2W and QW regimens), this should be considered when C_{trough} values derived from simulation are used for exposure comparison.

Model-Based Simulations

The simulations show that steady-state is achieved after approximately 12 (for C_{trough}) or 9 - 10 (for C_{mean}, AUC_{τ}, and C_{max}) weeks of dosing. The AUC_{τ} (and C_{mean}) accumulation ratios were 4.28 and 2.27 for 162 mg QW and Q2W SC regimens, respectively. The accumulation ratios for C_{trough} were 4.39 and 3.21, respectively. The accumulation ratios for the C_{max} were 3.66 and 1.88, respectively.

Due to dependence of total clearance on tocilizumab serum concentrations, half-life of tocilizumab is concentration-dependent and can only be calculated at a given serum concentration level. Based on conditional simulations, median effective half-life of tocilizumab during an inter-dose interval at steady-state varies between 12.2 and 13.5 days for 162 mg SC QW dosing (WT > 30 kg) and between 10.7 and 13.9 days for 162 mg SC Q2W dosing (WT < 30 kg). For Q2W IV regimens, it varies between 12.4 and 16.3 days for 8 mg/kg (WT > 30 kg) and between 10.3 and 16.1 days for 12 mg/kg (WT < 30 kg).

Comparison of predicted individual steady-state exposures (Table 24) following dosing regimens in studies WA18221 (8 and 12 mg/kg QW IV) and WA28118 (Q2W and QW 162 mg SC) showed that, distributions of predicted C_{trough} values were similar for IV and SC regimens and both weight groups (Figure 16). More than 95% (49/51) of predicted C_{trough} values for subjects in study WA28118 were above the 5th percentile of C_{trough} for subjects in study WA18221. This was also true for observed steady-state C_{trough} values collected at 12 weeks or later after starting treatment (Figure 17).

The range of predicted steady-state values of C_{mean} and AUC over 2 weeks were similar for the 2 weight groups following both IV and SC dosing, but the median values were lower for SC compared to IV dosing regimens (Figure 16). For subjects weighing ≥ 30 kg, the mean values of C_{mean} and AUC over 2 weeks were 23% lower following 162 mg SC QW compared to 8 mg/kg IV Q2W regimen. For subjects weighing < 30 kg, the mean values of C_{mean} and AUC over 2 weeks were 18% lower following 162 mg SC Q2W compared to 12 mg/kg IV Q2W regimen (Table 24).

As expected, C_{max} values were lower following SC administration compared to IV.

Reviewer's Comments: Overall, the population pharmacokinetic model developed using data from Study WA18221 and WA28118 was able to describe PK data after IV and SC

*TCZ administration from sJIA patients. However, PK parameters derived from model simulation should be used with caution, because 1) a tendency of under prediction the steady state C_{trough} concentrations following SC administration was observed in visual predictive check (*Figure 15*) discrepancy of model predicted parameters (AUC, C_{trough}, C_{max}) for the same study (WA18221) using the current model vs. the former population PK model was noted (refer to clinical pharmacology IR send on June 11 for more details).*

For the reasons provided above, the observed values should be used for steady state C_{trough} comparison between the two routes of tocilizumab administration. For both weight categories, the mean observed steady state C_{trough} following SC route are comparable to that following IV route (Table 25) with overlapped ranges (Table 25, Figure 17*).*

*For steady state AUC comparison using the predicted values, the mean values of AUC were about 25% lower following SC regimens compared to IV regiments by weight group (*Figure 16*). Given that a flat exposure-efficacy relationship was identified in the Phase 3 efficacy safety study for IV route in sJIA patients (Study WA18221), a 25% lower AUC is unlikely to result in compromised efficacy.*

Overall, the proposed SC regimens are acceptable from a Clinical Pharmacology perspective.

Table 24: Predicted Mean (SD) Steady-State Exposures by Dosing Regimen in Studies WA18221 and WA28118

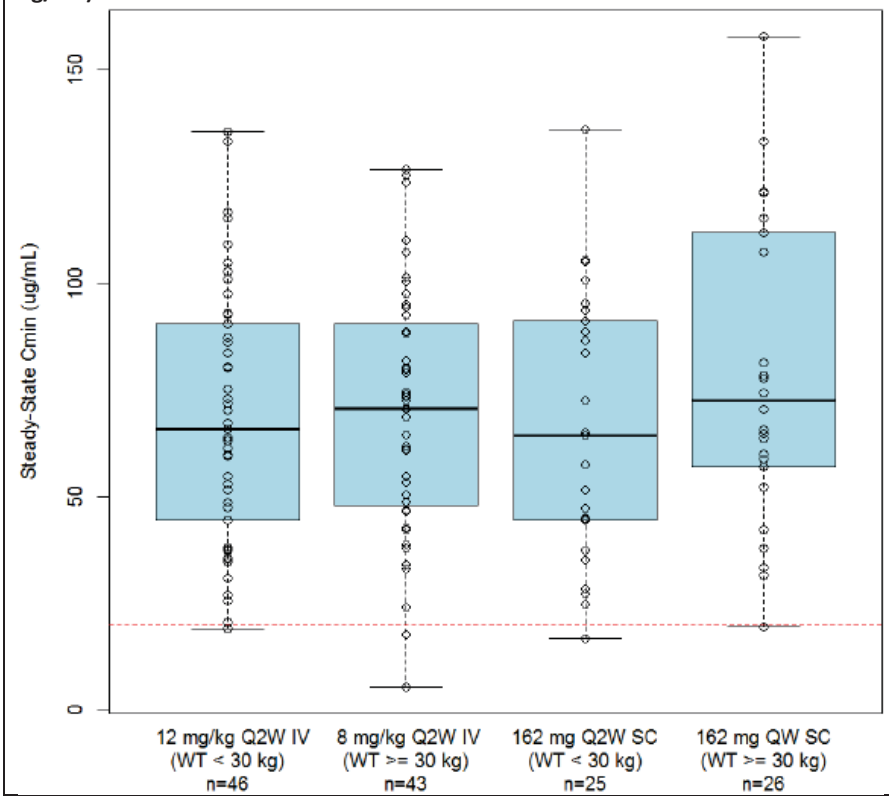
Concentration-time profiles were simulated from the model for all patients from studies WA18221 and WA28118 using their individual parameters predicted by the model (conditional simulations) and corresponding dosing regimens. Steady-state exposure values were computed and summarized by dosing regimens. $AUC_{2weeksSS}$ = steady-state AUC over 2 weeks.

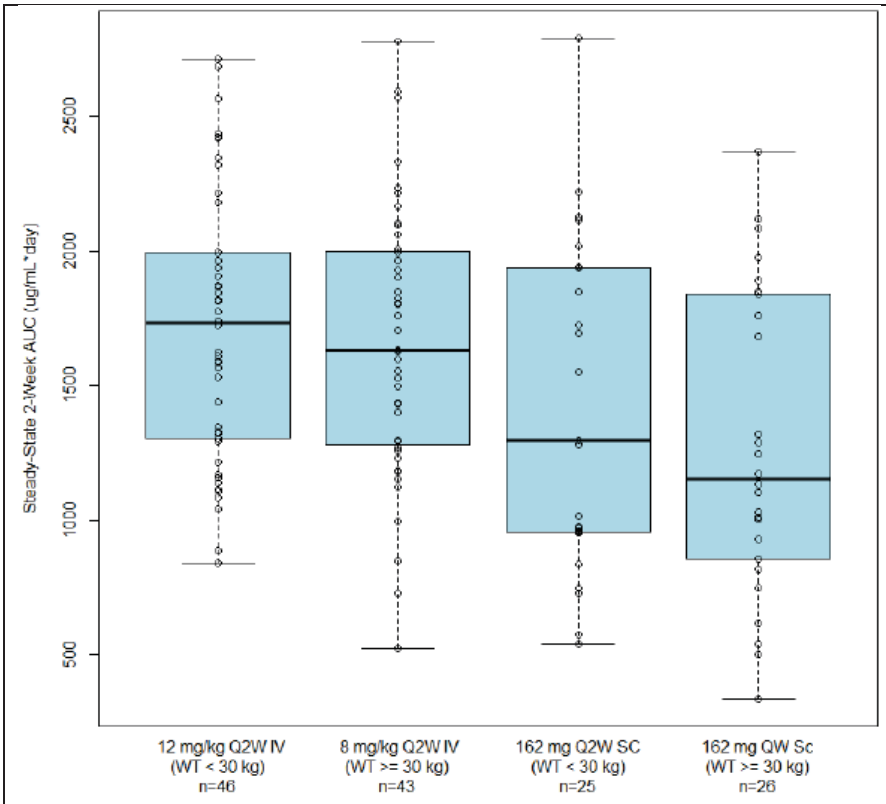
Dosing regimen	Weight Group	$C_{troughSS}$ (µg/mL)	C_{maxSS} (µg/mL)	C_{meanSS} (µg/mL)	$AUC_{2weeksSS}$ (µg/mL×day)
12 mg/kg IV Q2W (N=46)	WT < 30 kg	68.4 (29.97)	273.83 (63.8)	122.89 (36.04)	1721 (505)
8 mg/kg IV Q2W (N=43)	WT ≥ 30 kg	69.74 (29.1)	255.79 (60.77)	118.73 (36)	1662 (504)
162 mg SC Q2W (N=25)	WT < 30 kg	65.86 (31.31)	134.05 (58.64)	101.01 (43.22)	1414 (605)
162 mg SC QW (N=26)	WT ≥ 30 kg	79.18 (35.57)	99.75 (46.19)	91.28 (40.37)	1278 (565)

Source: Table 19 on Page 62 of 1084039.pdf

Figure 16: Distributions of Predicted Steady-State Trough Concentration Values (top) and AUC Values (bottom) for sJIA patients following IV and SC Dosing Regimens

Red dashed line: 5th percentile of predicted $C_{trough,SS}$ values for subjects from study WA18221 ($C_{troughSS}$= 20.2 ug/mL).

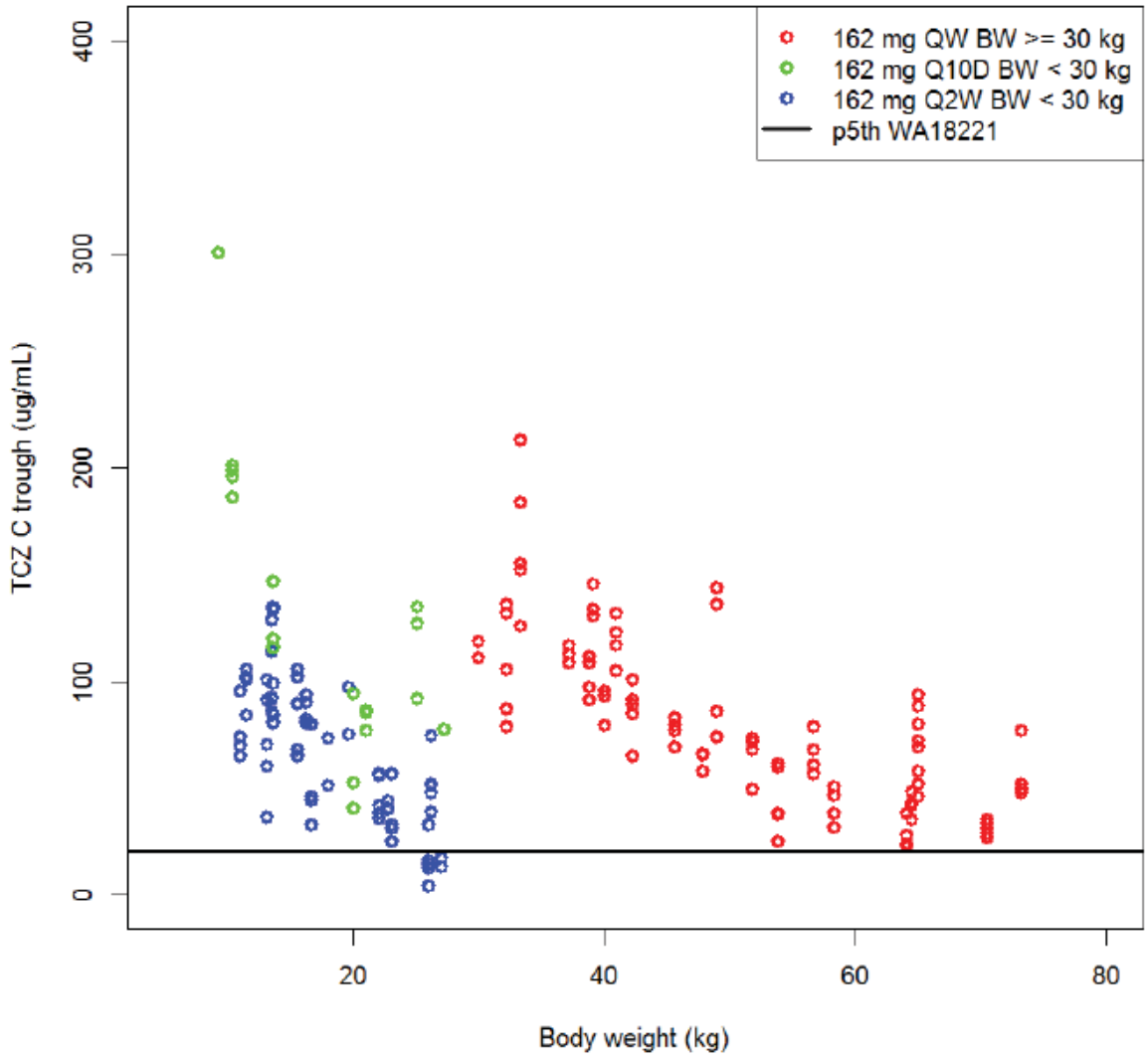




Source: Figure 53 and 55 of 1084039.pdf

Figure 17: Observed $C_{trough,SS}$ Values in Study WA28118 versus Weight: Original Scale

Observed $C_{trough,SS}$ values for study WA28118 (circles). They were defined as observations at week >12 after the first SC dose and at 3.5 - 10.5 days (for QW), 5 - 15 days (for Q10D) or 7 - 21 days (for Q2W) after the SC dose. Black line: 5th percentile of predicted $C_{trough,SS}$ values for subjects from study WA18221 ($C_{trough,SS}$=20.2 ug/mL).



Source: Figure 54 on Page 119 of 1084039.pdf

Table 25: Comparison of Observed Steady-state PK Data in Patients with sJIA in Studies WA18221 and WA28118 by Weight Category.

Body Weight < 30 kg				
Week	Time		WA28118 SC: 162 mg Q2W	WA18221 IV: 12 mg/kg Q2W
26	Pre-dose	N Mean±SD (min-max)	n=13 74.53 ± 32.76 (31.90 – 135.0)	n=40 74.75 ± 33.52 (16.90 – 172.0)
52	Pre-dose	N Mean±SD (min-max)	n=14 66.81 ± 27.65 (14.60 – 106.0)	n=39 67.68 ± 30.62 (6.06 – 115.0)
Body Weight ≥ 30 kg				
Week	Time		WA28118 SC: 162 mg QW	WA18221 IV: 8 mg/kg Q2W
26	Pre-dose	N Mean±SD (min-max)	n=22 74.67 ± 32.67 (24.20 – 146.0)	n=29 62.98 ± 27.59 (10.30 – 135.0)
52	Pre-dose	N Mean±SD (min-max)	n=20 74.25 ± 33.88 (27.10 – 155.0)	n=28 65.15 ± 26.34 (16.0 – 116.0)

Source: Sponsor's Response to IR sent on June 11, 2018
(\\cdsesub1\evsprod\bla125472\0193\m1\us\clin-response-fda-req-info.pdf)

Exposure - Safety Analysis

Observed trough concentrations and predicted steady state exposures were similar in subjects with and without events.

Results of the logistic regression showed that the probabilities for AEs were not significantly correlated with tocilizumab exposure for all safety events investigated.

Exposure -Efficacy Analysis

There were no consistent differences between treatments or prior TCZ status for attainment of inactive disease status. In each group, there were no differences between trough concentration-time courses of patients with and without inactive disease status at end of treatment.

For clinical remission, there were no differences between the treatment groups. While higher percent of prior TCZ patients attained clinical remission compared to TCZ-naive patients, confidence intervals were large and overlapping. In each group, there were no differences between trough concentration-time courses of patients who achieved and who did not achieve clinical remission.

Reviewer's Comments: Graphical analysis was mainly conducted to explore exposure-safety and exposure-efficacy relationship. No clear trends for the SC sJIA dose regimens were identified and it could possibly be explained by the small sample size (51 sJIA subjects) in study WA28118.

18.3.2. Reviewer's Analysis

The reviewer was able to reproduce the sponsor's results with NONMEM (Table 26, Table 27). No additional analysis was conducted.

Table 26: Analysis Codes/Datasets/Report

Study Number	Name	Link to EDR
Studies WA18221 and WA28118	Population PK Analysis of Tocilizumab SC and IV (WA28118 and WA18221) and Graphical Exposure-Safety and Exposure-Efficacy Analysis of Tocilizumab SC (WA28118) in Patients with Systemic Juvenile Idiopathic Arthritis (1084039.pdf)	\\cdsesub1\evsprod\BLA125472\0164\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\report-1084039\ 1084039.pdf
Studies WA18221 and WA28118	NONMEM control stream (run020-ctl.txt)	\\cdsesub1\evsprod\BLA125472\0164\m5\datasets\1084039\analysis\legacy\programs\run020-ctl.txt
Studies WA18221 and WA28118	NONMEM output file (run020-lst.txt)	\\cdsesub1\evsprod\BLA125472\0164\m5\datasets\1084039\analysis\legacy\programs\run020-lst.txt
Studies WA18221 and WA28118	Population PK dataset (poppk.xpt)	\\cdsesub1\evsprod\BLA125472\0164\m5\datasets\1084039\analysis\legacy\datasets\poppk.xpt
Studies WA18221 and WA28118	Response to FDA Request for Information submitted on June 18, 2018 (2018-06-18_ Clinical Response to FDA Request for Information.pdf)	\\cdsesub1\evsprod\bla125472\0193\m1\us\clin-response-fda-req-info.pdf

Table 27: Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Run020.mod	NONMEM control stream	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Tocilizumab_BLA125472_s031_JN\popPK_analysis_1084039\run020.mod
Run020.lst	NONMEM output file	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Tocilizumab_BLA125472_s031_JN\popPK_analysis_1084039\run020.lst

18.3.3. Sponsor's response to IR

Response to IR sent on June 11, 2018

INTRODUCTION

We refer to Hoffmann-La Roche Inc.'s Biologics License Application (BLA) 125472 approved on October 21, 2013 for the use of ACTEMRA subcutaneous (SC) to treat adults with moderately to severely active RA. Please also reference sBLA 125276/S-022, approved on April 15, 2011 for the treatment of systemic juvenile idiopathic arthritis (sJIA) patients intravenously with Actemra. Further reference is made to the efficacy supplement 125472/S-031 for treatment of sJIA patients with SC Actemra submitted on March 12, 2018.

The purpose of this submission is to formally provide the response to the Agency Request for Information received from FDA Project Manager Elaine Sit via e-mail on June 11, 2018.

QUESTION 1.

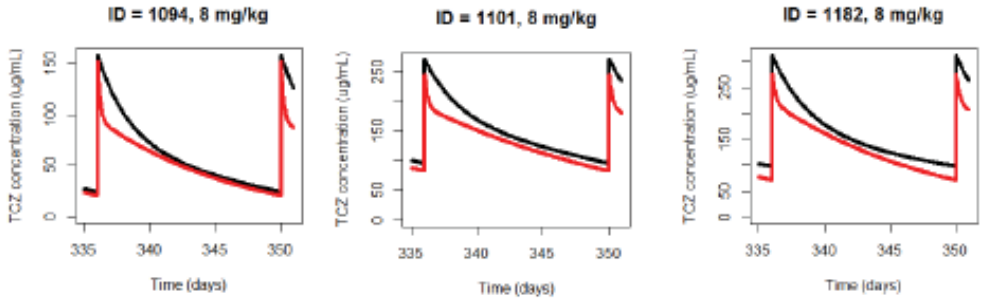
We have the following requests for information regarding the clinical report for Study WA28118 (Research Report Number 1079841):

Table 6 (page 56 of CSR of Study WA28118) lists the model predicted steady-state PK parameters for both IV and SC routes. The predicted median AUCs for IV route (Study WA18221) are 1734 and 1631 mcg·day/mL for patients with BW < 30 kg and ≥ 30 kg, respectively. However, in your submission dated October 14, 2010, for BLA 125276/S022 (tocilizumab IV for the treatment of sJIA), the model predicted mean AUCs for IV route (Study WA18221) were 1346 and 1337 mcg·day/mL for patients with BW < 30 kg and ≥ 30 kg, respectively [Table 40 in the CSR for Study WA18221 (Research Report Number 1035146)]. Different values were also observed for Cmin and Cmax at steady state. Explain the discrepancy of model predicted values for the same study (WA18221) in different reports and provide the values of the PK parameters that should be used for exposure comparison between the two routes of administration. Provide justification for your answer.

Company Response

The more recent population PK model based on the IV and SC data has been built on a more informative PK dataset compared to the former population PK model build only on the IV data. Indeed, the PK sampling was much richer following SC administration, allowing a better characterization of the disposition phases of tocilizumab. This is mainly reflected in the difference in the inter-compartmental clearance (i.e.: Q) between the IV and SC model (i.e. 0.354 L/day) versus the IV model (i.e.: 4.6 L/day). The consequence of this difference is illustrated in Figure 1 where the predicted steady-state PK profiles are compared between the 2 models for 3 illustrative patients who received tocilizumab via the IV route.

Figure 1 Selected Simulated Steady-State TCZ Concentration-Time Profiles (WA18221)



The TCZ concentration-time profiles shown in red are the individual predictions predicted by the previous model (Summary of Clinical Pharmacology, BLA 12276/S022). The TCZ concentration-time profiles shown in black are the individual predictions predicted by the current model (Summary of Clinical Pharmacology, BLA 125472S-031).

As shown by the above profiles, the main difference is a faster decline during the first days following the IV administration with the IV model compared to the IV and SC model. The consequence of this difference is a lower predicted AUC when using the IV PK model. The $C_{max,ss}$ and $C_{min,ss}$ are slightly different but those differences are minor. This is expected as PK samples were collected at the time of pre-dose (C_{min}) and post-IV infusion (C_{max}), and the 2 models are able to describe the IV data equally well.

For the reasons provided above, the secondary PK parameters provided in the current submission (Summary of Clinical Pharmacology, BLA 125472/S-031) should be used for exposure comparison between the two routes of TCZ administration.

QUESTION 2.

Summarize the observed PK data by treatment group in Studies WA18221 and WA28118. Provide the following results:

a) **Summary table(s) for the mean (SD) and median (range) concentration of tocilizumab by treatment group and time in Studies WA18221 and WA28118.**

b) **Plot mean PK (±SD) concentration-time profiles by treatment for WA18221 and WA28118 in the same graph. You may combine TCZ naïve patients and patients with prior TCZ exposure for this analysis. Provide results with and without the 162 mg SC Q10D regimen.**

Company Response

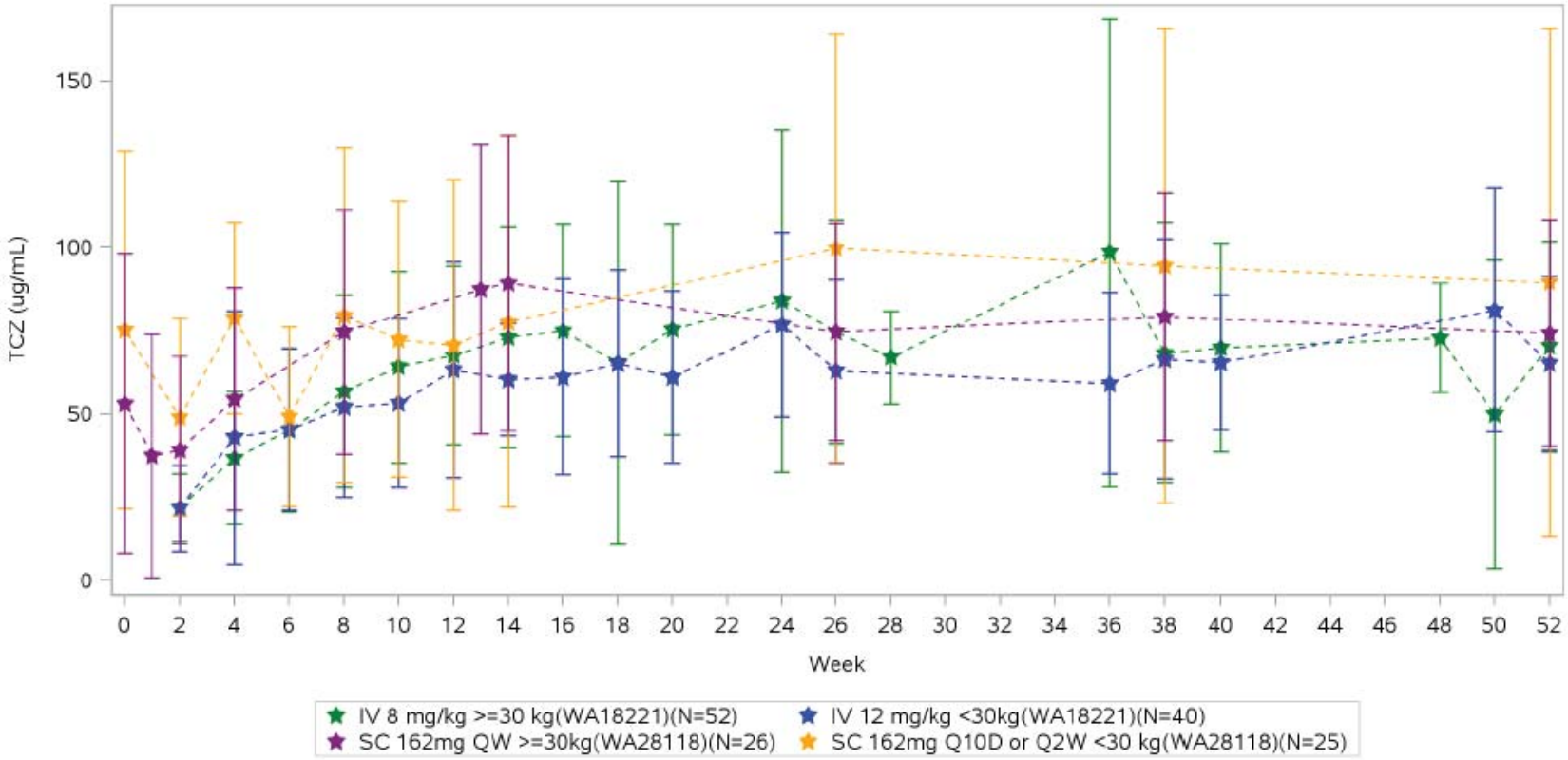
a. Summary tables for the mean (D) and median (range) of observed pre-dose concentration by treatment group are provided.

- For study WA18221, the summary table was included in the Week 104 CSR, pp16875. Output included (stlb10_pk_tpre).
- For study WA28118, the summary table with TCZ naïve patients and patients with prior TCZ exposure separated was included in the final CSR pp218. Output included (SA883_t_pk_SE_PK).
- For study WA28118, the summary tables with TCZ naïve patients and patients with prior TCZ exposure combined are included to this response, one with Q10D data included (SA1241_t_pk_SE_PK), one without Q10D data (SA1241_t_pk_exc_SE_PK).

b. Plots of observed pre-dose concentration time profile including both the IV and SC treatment are provided. TCZ naïve patients and patients with prior TCZ exposure are combined. (SA1241_g_ef_SE_PK, SA1241_g_ef_exc_SE_PK)

Mean (± SD) Pre-dose Serum TCZ Concentration Time-Profile by Treatment Group from Baseline to Week 52, Safety Population

Protocol: WA18221 and WA28118

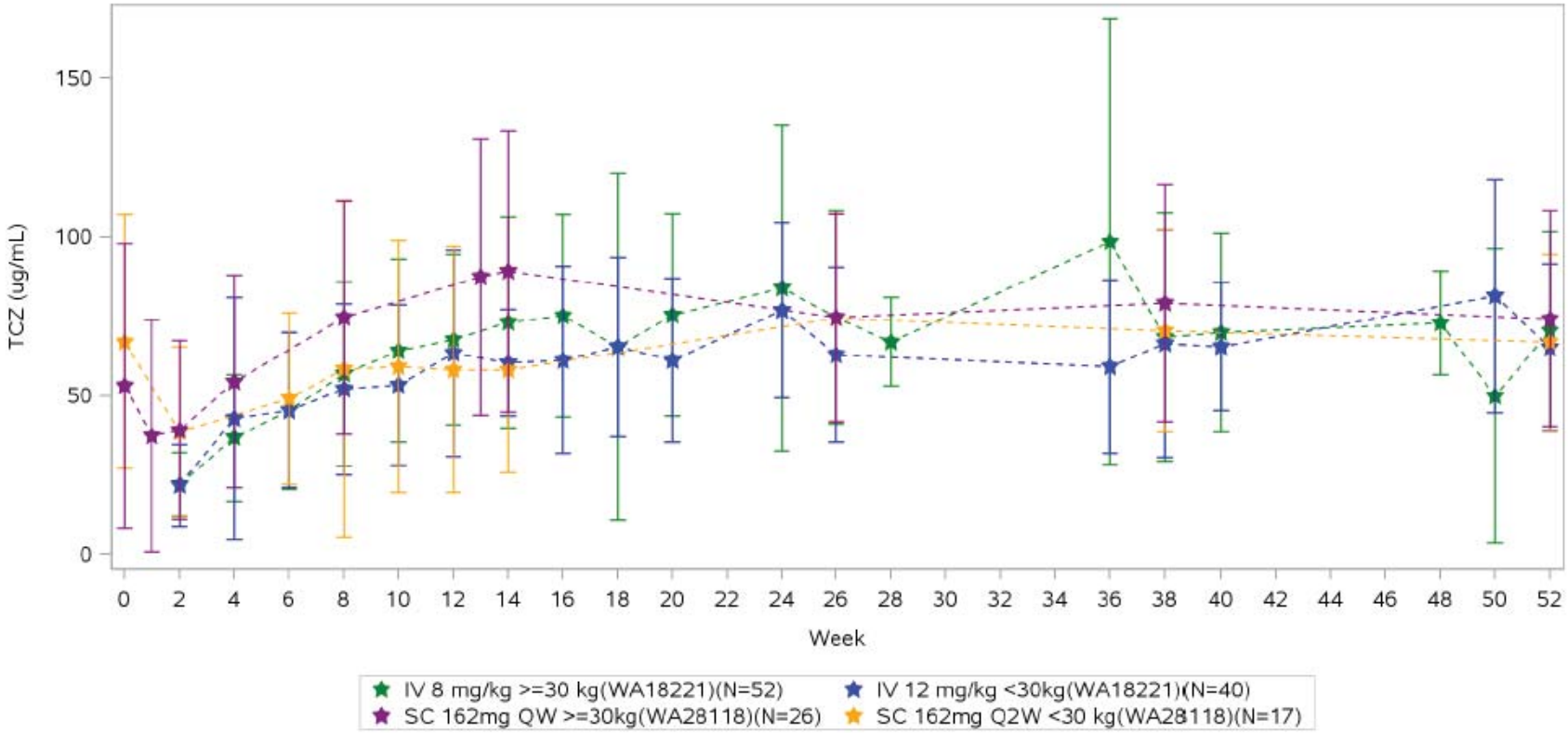


Summary data for visits with n=1 were not included.
Excluded baseline data for the IV data.
Excluded switcher patients for the IV data.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_g_ef.sas Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_g_ef_SE_PK.pdf
15JUN2018 9:03

Mean (± SD) Pre-dose Serum TCZ Concentration Time-Profile by Treatment Group from Baseline to Week 52, Safety Population

Protocol: WA18221 and WA28118



Summary data for visits with n=1 were not included.
Data for Q10D patients have been excluded.
Excluded baseline data for the IV data.
Excluded switcher patients for the IV data.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_g_ef_exc.sas Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_g_ef_exc_SE_PK.pdf 15JUN2018 9:07

Pharmacokinetic Results by Visit excluding Q10D patients, Safety Population
Protocol: WA28118

Parameter: Serum TCZ Concentration (ug/mL)

	TCZ SC 162 mg Q2W (< 30 kg) (N=17)	TCZ SC 162 mg QW (>= 30 kg) (N=26)	All TCZ (N=43)
Visit	Value at Visit	Value at Visit	Value at Visit
Baseline			
n	4	12	16
Mean (SD)	67.000 (39.888)	53.175 (44.880)	56.631 (42.820)
Median	81.150	42.450	49.400
Min - Max	10.00 - 95.70	1.19 - 124.00	1.19 - 124.00
Week 1			
n	0	25	25
Mean (SD)	NE (NE)	37.476 (36.573)	37.476 (36.573)
Median	NE	23.300	23.300
Min - Max	NE - NE	1.12 - 114.00	1.12 - 114.00
Week 2			
n	15	22	37
Mean (SD)	38.722 (26.820)	39.209 (28.201)	39.011 (27.271)
Median	32.400	28.650	30.900
Min - Max	0.89 - 91.80	10.50 - 98.10	0.89 - 98.10
Week 4			
n	0	25	25
Mean (SD)	NE (NE)	54.436 (33.425)	54.436 (33.425)
Median	NE	46.900	46.900
Min - Max	NE - NE	4.41 - 130.00	4.41 - 130.00
Week 6			
n	14	0	14
Mean (SD)	49.236 (27.023)	NE (NE)	49.236 (27.023)
Median	48.950	NE	48.950
Min - Max	2.02 - 86.80	NE - NE	2.02 - 86.80
Week 8			
n	10	24	34
Mean (SD)	58.440 (52.735)	74.696 (36.696)	69.915 (41.875)
Median	44.000	74.850	65.150
Min - Max	6.78 - 180.00	31.70 - 172.00	6.78 - 180.00
Week 10			
n	14	0	14
Mean (SD)	59.200 (39.645)	NE (NE)	59.200 (39.645)
Median	52.900	NE	52.900
Min - Max	10.20 - 127.00	NE - NE	10.20 - 127.00

Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_t_pk_exc.sas
Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_t_pk_exc_SE_PK.out
13JUN2018 13:41

Pharmacokinetic Results by Visit excluding Q10D patients, Safety Population
Protocol: WA28118

Parameter: Serum TCZ Concentration (ug/mL)

Visit	TCZ SC 162 mg Q2W (< 30 kg) (N=17) Value at Visit	TCZ SC 162 mg QW (>= 30 kg) (N=26) Value at Visit	All TCZ (N=43) Value at Visit
Week 12			
n	14	0	14
Mean (SD)	58.257 (38.677)	NE (NE)	58.257 (38.677)
Median	42.500	NE	42.500
Min - Max	13.20 - 134.00	NE - NE	13.20 - 134.00
Week 13			
n	0	13	13
Mean (SD)	NE (NE)	87.400 (43.483)	87.400 (43.483)
Median	NE	69.200	69.200
Min - Max	NE - NE	31.20 - 184.00	31.20 - 184.00
Week 14			
n	16	20	36
Mean (SD)	58.238 (32.282)	89.240 (44.391)	75.461 (41.958)
Median	43.900	83.100	73.350
Min - Max	12.80 - 114.00	28.10 - 213.00	12.80 - 213.00
Week 26			
n	13	22	35
Mean (SD)	74.531 (32.758)	74.668 (32.670)	74.617 (32.217)
Median	70.800	75.600	72.400
Min - Max	31.90 - 135.00	24.20 - 146.00	24.20 - 146.00
Week 38			
n	15	23	38
Mean (SD)	70.445 (31.877)	79.300 (37.301)	75.805 (35.086)
Median	80.300	76.000	78.150
Min - Max	4.58 - 122.00	22.70 - 152.00	4.58 - 152.00
Week 52			
n	14	20	34
Mean (SD)	66.807 (27.645)	74.250 (33.877)	71.185 (31.235)
Median	74.850	67.300	74.050
Min - Max	14.60 - 106.00	27.10 - 155.00	14.60 - 155.00

Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_t_pk_exc.sas
Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_t_pk_exc_SE_PK.out
13JUN2018 13:41

Pharmacokinetic Results by Visit, Safety Population
Protocol: WA28118

Parameter: Serum TCZ Concentration (ug/mL)

	TCZ SC 162 mg Q10D or Q2W (< 30 kg) (N=25)	TCZ SC 162 mg QW (>= 30 kg) (N=26)	All TCZ (N=51)
Visit	Value at Visit	Value at Visit	Value at Visit
Baseline			
n	7	12	19
Mean (SD)	75.186 (53.676)	53.175 (44.880)	61.284 (48.066)
Median	68.900	42.450	55.500
Min - Max	10.00 - 172.00	1.19 - 124.00	1.19 - 172.00
Week 1			
n	0	25	25
Mean (SD)	NE (NE)	37.476 (36.573)	37.476 (36.573)
Median	NE	23.300	23.300
Min - Max	NE - NE	1.12 - 114.00	1.12 - 114.00
Week 2			
n	23	22	45
Mean (SD)	49.110 (29.782)	39.209 (28.201)	44.269 (29.122)
Median	49.500	28.650	38.200
Min - Max	0.89 - 110.00	10.50 - 98.10	0.89 - 110.00
Week 4			
n	8	25	33
Mean (SD)	78.838 (28.717)	54.436 (33.425)	60.352 (33.631)
Median	82.200	46.900	54.300
Min - Max	36.10 - 123.00	4.41 - 130.00	4.41 - 130.00
Week 6			
n	14	0	14
Mean (SD)	49.236 (27.023)	NE (NE)	49.236 (27.023)
Median	48.950	NE	48.950
Min - Max	2.02 - 86.80	NE - NE	2.02 - 86.80
Week 8			
n	18	24	42
Mean (SD)	79.633 (50.171)	74.696 (36.696)	76.812 (42.488)
Median	75.100	74.850	74.850
Min - Max	6.78 - 180.00	31.70 - 172.00	6.78 - 180.00
Week 10			
n	21	0	21
Mean (SD)	72.476 (41.365)	NE (NE)	72.476 (41.365)
Median	74.900	NE	74.900
Min - Max	10.20 - 139.00	NE - NE	10.20 - 139.00

Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_t_pk.sas
Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_t_pk_SE_PK.out
13JUN2018 13:40

Pharmacokinetic Results by Visit, Safety Population
Protocol: WA28118

Parameter: Serum TCZ Concentration (ug/mL)

Visit	TCZ SC 162 mg Q10D (< 30 kg) (N=8) Value at Visit	TCZ SC 162 mg Q2W (< 30 kg) (N=17) Value at Visit
Baseline		
n	3	4
Mean (SD)	86.100 (77.098)	67.000 (39.888)
Median	63.400	81.150
Min - Max	22.90 - 172.00	10.00 - 95.70
Week 1		
n	0	0
Mean (SD)	NE (NE)	NE (NE)
Median	NE	NE
Min - Max	NE - NE	NE - NE
Week 2		
n	8	15
Mean (SD)	68.588 (26.156)	38.722 (26.820)
Median	72.250	32.400
Min - Max	23.80 - 110.00	0.89 - 91.80
Week 4		
n	8	0
Mean (SD)	78.838 (28.717)	NE (NE)
Median	82.200	NE
Min - Max	36.10 - 123.00	NE - NE
Week 6		
n	0	14
Mean (SD)	NE (NE)	49.236 (27.023)
Median	NE	48.950
Min - Max	NE - NE	2.02 - 86.80
Week 8		
n	8	10
Mean (SD)	106.125 (33.073)	58.440 (52.735)
Median	104.000	44.000
Min - Max	68.80 - 155.00	6.78 - 180.00
Week 10		
n	7	14
Mean (SD)	99.029 (32.623)	59.200 (39.645)
Median	76.500	52.900
Min - Max	67.70 - 139.00	10.20 - 127.00

Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_t_pk.sas
Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_t_pk_SE_PK.out
13JUN2018 13:40

Pharmacokinetic Results by Visit, Safety Population
Protocol: WA28118

Parameter: Serum TCZ Concentration (ug/mL)

Visit	TCZ SC 162 mg Q10D or Q2W (< 30 kg) (N=25) Value at Visit	TCZ SC 162 mg QW (>= 30 kg) (N=26) Value at Visit	All TCZ (N=51) Value at Visit
Week 12			
n	19	0	19
Mean (SD)	70.721 (49.623)	NE (NE)	70.721 (49.623)
Median	47.900	NE	47.900
Min - Max	13.20 - 196.00	NE - NE	13.20 - 196.00
Week 13			
n	0	13	13
Mean (SD)	NE (NE)	87.400 (43.483)	87.400 (43.483)
Median	NE	69.200	69.200
Min - Max	NE - NE	31.20 - 184.00	31.20 - 184.00
Week 14			
n	23	20	43
Mean (SD)	77.678 (55.728)	89.240 (44.391)	83.056 (50.520)
Median	69.800	83.100	77.800
Min - Max	12.80 - 256.00	28.10 - 213.00	12.80 - 256.00
Week 26			
n	19	22	41
Mean (SD)	99.879 (64.156)	74.668 (32.670)	86.351 (50.740)
Median	92.100	75.600	78.800
Min - Max	31.90 - 301.00	24.20 - 146.00	24.20 - 301.00
Week 38			
n	21	23	44
Mean (SD)	94.685 (71.106)	79.300 (37.301)	86.643 (55.892)
Median	86.000	76.000	83.550
Min - Max	4.58 - 347.00	22.70 - 152.00	4.58 - 347.00
Week 52			
n	18	20	38
Mean (SD)	89.644 (76.145)	74.250 (33.877)	81.542 (57.567)
Median	77.900	67.300	74.850
Min - Max	14.60 - 369.00	27.10 - 155.00	14.60 - 369.00

Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_t_pk.sas
Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_t_pk_SE_PK.out
13JUN2018 13:40

Pharmacokinetic Results by Visit, Safety Population
Protocol: WA28118

Parameter: Serum TCZ Concentration (ug/mL)

Visit	TCZ SC 162 mg Q10D (< 30 kg) (N=8) Value at Visit	TCZ SC 162 mg Q2W (< 30 kg) (N=17) Value at Visit
Week 12		
n	5	14
Mean (SD)	105.620 (64.445)	58.257 (38.677)
Median	85.300	42.500
Min - Max	42.50 - 196.00	13.20 - 134.00
Week 13		
n	0	0
Mean (SD)	NE (NE)	NE (NE)
Median	NE	NE
Min - Max	NE - NE	NE - NE
Week 14		
n	7	16
Mean (SD)	122.114 (73.963)	58.238 (32.282)
Median	91.800	43.900
Min - Max	40.70 - 256.00	12.80 - 114.00
Week 26		
n	6	13
Mean (SD)	154.800 (83.380)	74.531 (32.758)
Median	127.500	70.800
Min - Max	77.10 - 301.00	31.90 - 135.00
Week 38		
n	6	15
Mean (SD)	155.283 (105.876)	70.445 (31.877)
Median	123.500	80.300
Min - Max	52.50 - 347.00	4.58 - 122.00
Week 52		
n	4	14
Mean (SD)	169.575 (136.352)	66.807 (27.645)
Median	124.500	74.850
Min - Max	60.30 - 369.00	14.60 - 106.00

Baseline is the patient's last observation prior to initiation of study drug.

Program: /opt/BIOSTAT/prod/cn11935d/i28118b/SA1241_t_pk.sas
Output: /opt/BIOSTAT/prod/cn11935d/i28118b/reports/SA1241_t_pk_SE_PK.out
13JUN2018 13:40

stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Baseline n	Mean	SD	Median	Min	Max
Treatment: TCZ 8 MG/KG (N = 52)													
	BASELINE	1	0.11		0.11	0.11	0.11						
	WEEK 2	39	22.05	10.010	20.10	0.11	47.00	1	21.49		21.49	21.49	21.49
	WEEK 4	39	36.87	19.914	32.40	0.85	91.20	1	31.49		31.49	31.49	31.49
	WEEK 6	39	45.28	24.569	45.30	3.37	125.00	0					
	WEEK 8	44	56.91	28.929	57.90	1.94	128.00	1	58.09		58.09	58.09	58.09
	WEEK 10	39	64.17	28.768	65.20	5.79	136.00	1	58.99		58.99	58.99	58.99
	WEEK 12	36	67.72	26.867	66.30	9.56	120.00	1	58.49		58.49	58.49	58.49
	WEEK 14	8	73.11	33.228	75.35	9.99	130.00	0					
	WEEK 16	36	75.14	31.835	70.75	19.40	148.00	1	72.79		72.79	72.79	72.79
	WEEK 18	3	65.39	54.560	69.10	9.07	118.00	0					
	WEEK 20	34	75.41	31.708	75.55	16.00	164.00	1	88.59		88.59	88.59	88.59
	WEEK 22	1	39.60		39.60	39.60	39.60	0					
	WEEK 24	4	83.98	51.335	97.75	12.40	128.00	0					
	WEEK 26	40	74.75	33.520	74.00	16.90	172.00	1	72.19		72.19	72.19	72.19
	WEEK 28	2	67.05	13.930	67.05	57.20	76.90	0					
	WEEK 32	1	38.60		38.60	38.60	38.60	0					
	WEEK 34	1	68.70		68.70	68.70	68.70	0					
	WEEK 36	4	98.55	70.288	105.45	15.30	168.00	0					
	WEEK 38	31	67.81	39.495	61.20	1.70	145.00	1	69.39		69.39	69.39	69.39
	WEEK 40	8	69.95	31.269	65.65	36.30	134.00	0					
	WEEK 42	1	65.10		65.10	65.10	65.10	0					
	WEEK 46	1	38.20		38.20	38.20	38.20	0					
	WEEK 48	2	72.95	16.334	72.95	61.40	84.50	0					
	WEEK 50	4	49.90	46.282	42.65	6.30	108.00	0					
	WEEK 52	39	67.68	30.617	63.80	6.06	115.00	1	63.19		63.19	63.19	63.19
	WEEK 54	1	61.50		61.50	61.50	61.50	0					
	WEEK 58	1	41.20		41.20	41.20	41.20	0					
	WEEK 60	2	41.70	30.971	41.70	19.80	63.60	0					
	WEEK 62	4	71.50	61.349	55.05	17.90	158.00	0					
	WEEK 64	29	70.62	35.825	70.60	9.88	166.00	1	74.69		74.69	74.69	74.69

(TT group continuing ...)

Change from baseline values includes only those patients with both a baseline value and a value for summarized time period.
n represents number of patients contributing to summary statistics.
All values have been converted to SI units.
Baseline considered to be first dose of TCZ treatment.
LB10 06OCT2011:11:57:04 (1 of 8)

stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Baseline n	Mean	SD	Median	Min	Max
(... TT group continuing)													
Treatment: TCZ 8 MG/KG (N = 52)													
	WEEK 66	6	60.19	46.118	81.85	0.10	97.80	0					
	WEEK 68	2	58.40	3.253	58.40	56.10	60.70	0					
	WEEK 72	1	45.10		45.10	45.10	45.10	0					
	WEEK 74	2	49.75	30.193	49.75	28.40	71.10	0					
	WEEK 76	3	62.50	35.285	51.40	34.10	102.00	0					
	WEEK 78	32	75.60	32.552	75.45	0.41	148.00	1	18.39		18.39	18.39	18.39
	WEEK 80	2	62.55	8.415	62.55	56.60	68.50	0					
	WEEK 84	1	61.70		61.70	61.70	61.70	0					
	WEEK 86	2	68.95	1.344	68.95	68.00	69.90	0					
	WEEK 88	3	63.20	51.194	52.20	18.40	119.00	0					
	WEEK 90	27	71.03	33.754	70.50	0.45	125.00	0					
	WEEK 92	5	82.80	14.139	82.40	60.60	97.50	0					
	WEEK 94	2	48.45	11.809	48.45	40.10	56.80	0					
	WEEK 100	2	28.10	4.525	28.10	24.90	31.30	0					
	WEEK 102	2	47.10	49.639	47.10	12.00	82.20	0					
	WEEK 104	28	70.19	40.177	75.05	0.50	138.00	1	74.19		74.19	74.19	74.19

Change from baseline values includes only those patients with both a baseline value and a value for summarized time period.
n represents number of patients contributing to summary statistics.
All values have been converted to SI units.
Baseline considered to be first dose of TCZ treatment.
LB10 06OCT2011:11:57:04 (2 of 8)

stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Baseline n	Mean	SD	Median	Min	Max
Treatment: TCZ 12 MG/KG (N = 40)													
	BASELINE	2	213.50	108.187	213.50	137.00	290.00						
	WEEK 2	28	21.76	12.975	17.45	6.48	55.50	2	-196.55	114.905	-196.55	-277.80	-115.30
	WEEK 4	31	42.92	38.042	35.20	3.24	224.00	1	-99.90		-99.90	-99.90	-99.90
	WEEK 6	27	45.41	24.399	44.40	3.62	101.00	2	-161.75	104.723	-161.75	-235.80	-87.70
	WEEK 8	33	52.06	26.985	51.00	0.16	106.00	1	-81.80		-81.80	-81.80	-81.80
	WEEK 10	27	53.39	25.380	56.90	4.24	106.00	1	-88.30		-88.30	-88.30	-88.30
	WEEK 12	23	63.31	32.495	59.70	4.99	123.00	1	-90.90		-90.90	-90.90	-90.90
	WEEK 14	12	60.44	16.869	61.80	29.90	89.10	0					
	WEEK 16	24	61.27	29.492	54.40	1.96	110.00	2	-148.60	96.167	-148.60	-216.60	-80.60
	WEEK 18	7	65.31	28.114	48.00	41.80	116.00	0					
	WEEK 20	24	61.19	25.795	55.60	28.40	130.00	2	-150.15	105.854	-150.15	-225.00	-75.30
	WEEK 22	1	120.00		120.00	120.00	120.00	0					
	WEEK 24	7	76.93	27.598	70.40	53.90	134.00	0					
	WEEK 26	29	62.98	27.585	63.20	10.30	135.00	2	-149.05	109.955	-149.05	-226.80	-71.30
	WEEK 28	1	12.50		12.50	12.50	12.50	0					
	WEEK 34	1	124.00		124.00	124.00	124.00	0					
	WEEK 36	7	59.27	27.304	57.10	19.60	100.00	0					
	WEEK 38	19	66.47	35.876	60.60	1.24	164.00	2	-168.75	142.199	-168.75	-269.30	-68.20
	WEEK 40	5	65.54	20.156	57.10	44.70	96.20	0					
	WEEK 48	1	109.00		109.00	109.00	109.00	0					
	WEEK 50	7	81.34	36.574	75.80	40.00	139.00	0					
	WEEK 52	28	65.15	26.344	62.80	16.00	116.00	2	-168.45	134.421	-168.45	-263.50	-73.40
	WEEK 58	1	6.13		6.13	6.13	6.13	0					
	WEEK 60	2	71.80	37.477	71.80	45.30	98.30	0					
	WEEK 62	7	78.79	22.091	68.20	51.80	110.00	0					
	WEEK 64	21	69.32	27.349	76.10	19.40	115.00	2	-141.35	114.905	-141.35	-222.60	-60.10
	WEEK 66	6	75.68	36.196	63.75	43.30	145.00	0					
	WEEK 74	1	117.00		117.00	117.00	117.00	0					
	WEEK 76	6	61.25	35.342	62.05	10.50	114.00	0					
	WEEK 78	25	74.02	50.682	63.70	2.40	269.00	2	-155.85	54.518	-155.85	-194.40	-117.30

(TT group continuing ...)

Change from baseline values includes only those patients with both a baseline value and a value for summarized time period.
n represents number of patients contributing to summary statistics.
All values have been converted to SI units.
Baseline considered to be first dose of TCZ treatment.
LB10 06OCT2011:11:57:04 (3 of 8)

stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Baseline n	Mean	SD	Median	Min	Max
(... TT group continuing)													
Treatment: TCZ 12 MG/KG (N = 40)													
	WEEK 86	1	102.00		102.00	102.00	102.00	0					
	WEEK 88	5	62.72	31.509	58.40	22.60	110.00	0					
	WEEK 90	17	71.54	58.745	64.90	0.13	262.00	2	-163.25	129.754	-163.25	-255.00	-71.50
	WEEK 92	5	57.82	14.919	65.40	39.60	73.20	0					
	WEEK 100	1	98.50		98.50	98.50	98.50	0					
	WEEK 102	6	73.92	37.592	63.45	34.50	131.00	0					
	WEEK 104	19	70.62	36.704	71.80	4.18	129.00	2	-168.65	143.331	-168.65	-270.00	-67.30

Change from baseline values includes only those patients with both a baseline value and a value for summarized time period.
n represents number of patients contributing to summary statistics.
All values have been converted to SI units.
Baseline considered to be first dose of TCZ treatment.
LB10 06OCT2011:11:57:04 (4 of 8)

stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Baseline n	Mean	SD	Median	Min	Max
Treatment: TCZ Switchers (N = 20)													
	BASELINE	1	6.22		6.22	6.22	6.22						
	WEEK 2	17	25.15	11.922	21.10	10.20	49.10	1	12.28		12.28	12.28	12.28
	WEEK 4	15	44.01	23.434	41.40	0.59	80.60	1	34.28		34.28	34.28	34.28
	WEEK 6	14	56.53	17.971	57.25	20.10	83.60	0					
	WEEK 8	17	61.52	21.397	62.90	19.70	101.00	1	25.18		25.18	25.18	25.18
	WEEK 10	15	72.19	22.281	66.10	37.80	110.00	0					
	WEEK 12	14	77.27	30.673	76.10	33.50	149.00	1	27.28		27.28	27.28	27.28
	WEEK 14	5	82.58	26.073	93.40	52.60	111.00	0					
	WEEK 16	13	81.15	40.705	62.80	13.00	163.00	0					
	WEEK 18	2	98.05	50.841	98.05	62.10	134.00	1	55.88		55.88	55.88	55.88
	WEEK 20	14	76.90	40.607	72.80	13.80	151.00	0					
	WEEK 24	2	73.60	26.729	73.60	54.70	92.50	0					
	WEEK 26	15	64.03	34.596	55.30	13.80	129.00	0					
	WEEK 30	1	67.40		67.40	67.40	67.40	1	61.18		61.18	61.18	61.18
	WEEK 32	1	62.20		62.20	62.20	62.20	0					
	WEEK 36	1	87.60		87.60	87.60	87.60	0					
	WEEK 38	14	71.88	52.669	62.20	2.90	214.00	0					
	WEEK 40	2	44.60	2.828	44.60	42.60	46.60	0					
	WEEK 44	1	254.00		254.00	254.00	254.00	1	247.78		247.78	247.78	247.78
	WEEK 46	1	71.10		71.10	71.10	71.10	0					
	WEEK 50	2	94.10	36.628	94.10	68.20	120.00	0					
	WEEK 52	15	74.64	35.091	72.70	2.67	140.00	0					
	WEEK 56	1	78.60		78.60	78.60	78.60	1	72.38		72.38	72.38	72.38
	WEEK 58	1	0.65		0.65	0.65	0.65	0					
	WEEK 62	1	69.70		69.70	69.70	69.70	0					
	WEEK 64	13	65.79	27.288	72.80	16.70	111.00	0					
	WEEK 66	2	36.15	21.850	36.15	20.70	51.60	0					
	WEEK 70	1	81.30		81.30	81.30	81.30	1	75.08		75.08	75.08	75.08
	WEEK 76	3	39.79	33.250	56.80	1.48	61.10	0					
	WEEK 78	13	60.70	32.750	51.00	6.05	123.00	0					

(TT group continuing ...)

Change from baseline values includes only those patients with both a baseline value and a value for summarized time period.
n represents number of patients contributing to summary statistics.
All values have been converted to SI units.
Baseline considered to be first dose of TCZ treatment.
LB10 06OCT2011:11:57:04 (5 of 8)

stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Baseline n	Mean	SD	Median	Min	Max
(... TT group continuing)													
Treatment: TCZ Switchers (N = 20)													
	WEEK 88	1	51.40		51.40	51.40	51.40	0					
	WEEK 90	10	67.17	40.579	62.75	7.01	125.00	0					
	WEEK 92	2	54.40	5.798	54.40	50.30	58.50	0					
	WEEK 96	1	33.60		33.60	33.60	33.60	1	27.38		27.38	27.38	27.38
	WEEK 98	1	78.70		78.70	78.70	78.70	0					
	WEEK 102	1	22.90		22.90	22.90	22.90	0					
	WEEK 104	10	53.08	26.164	52.20	13.50	83.30	0					

Change from baseline values includes only those patients with both a baseline value and a value for summarized time period.
n represents number of patients contributing to summary statistics.
All values have been converted to SI units.
Baseline considered to be first dose of TCZ treatment.
LB10 06OCT2011:11:57:04 (6 of 8)

stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Baseline n	Mean	SD	Median	Min	Max
Treatment: All TCZ (N = 112)													
	BASELINE	4	108.33	136.581	71.61	0.11	290.00						
	WEEK 2	84	22.58	11.391	19.80	0.11	55.50	4	-89.83	139.999	-51.51	-277.80	21.49
	WEEK 4	85	40.34	28.253	35.50	0.59	224.00	3	-11.38	76.675	31.49	-99.90	34.28
	WEEK 6	80	47.29	23.617	47.00	3.37	125.00	2	-161.75	104.723	-161.75	-235.80	-87.70
	WEEK 8	94	56.04	26.976	56.10	0.16	128.00	3	0.49	73.139	25.18	-81.80	58.09
	WEEK 10	81	62.06	27.131	61.90	4.24	136.00	2	-14.66	104.147	-14.66	-88.30	58.99
	WEEK 12	73	68.16	29.448	64.70	4.99	149.00	3	-1.71	78.800	27.28	-90.90	58.49
	WEEK 14	25	68.92	25.425	66.40	9.99	130.00	0					
	WEEK 16	73	71.65	33.240	67.50	1.96	163.00	3	-74.80	144.780	-80.60	-216.60	72.79
	WEEK 18	12	70.79	37.006	65.60	9.07	134.00	1	55.88		55.88	55.88	55.88
	WEEK 20	72	70.96	32.148	65.15	13.80	164.00	3	-70.57	156.846	-75.30	-225.00	88.59
	WEEK 22	2	79.80	56.851	79.80	39.60	120.00	0					
	WEEK 24	13	78.58	33.386	74.60	12.40	134.00	0					
	WEEK 26	84	68.77	31.931	66.55	10.30	172.00	3	-75.30	149.533	-71.30	-226.80	72.19
	WEEK 28	3	48.87	32.999	57.20	12.50	76.90	0					
	WEEK 30	1	67.40		67.40	67.40	67.40	1	61.18		61.18	61.18	61.18
	WEEK 32	2	50.40	16.688	50.40	38.60	62.20	0					
	WEEK 34	2	96.35	39.103	96.35	68.70	124.00	0					
	WEEK 36	12	74.73	46.125	64.95	15.30	168.00	0					
	WEEK 38	64	68.30	41.072	60.90	1.24	214.00	3	-89.37	170.333	-68.20	-269.30	69.39
	WEEK 40	15	65.10	26.059	57.10	36.30	134.00	0					
	WEEK 42	1	65.10		65.10	65.10	65.10	0					
	WEEK 44	1	254.00		254.00	254.00	254.00	1	247.78		247.78	247.78	247.78
	WEEK 46	2	54.65	23.264	54.65	38.20	71.10	0					
	WEEK 48	3	84.97	23.803	84.50	61.40	109.00	0					
	WEEK 50	13	73.63	40.105	68.20	6.30	139.00	0					
	WEEK 52	82	68.09	29.916	66.05	2.67	140.00	3	-91.24	164.072	-73.40	-263.50	63.19
	WEEK 54	1	61.50		61.50	61.50	61.50	0					
	WEEK 56	1	78.60		78.60	78.60	78.60	1	72.38		72.38	72.38	72.38
	WEEK 58	3	15.99	22.000	6.13	0.65	41.20	0					

(TT group continuing ...)

Change from baseline values includes only those patients with both a baseline value and a value for summarized time period.
n represents number of patients contributing to summary statistics.
All values have been converted to SI units.
Baseline considered to be first dose of TCZ treatment.
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stlb10_pk_tpre TCZ Serum Concentration (Pre-Dose) at Visits (Safety Population)
Protocol(s): WA18221 (H18221A)
Analysis: SAFETY Center: ALL CENTERS
Class: MISCELLANEOUS

TCZ Serum Concentration (ug/mL)
(Standard Reference Range: n.d. - n.d.)

Analysis Group	Scheduled Visit	Actual Values n	Mean	SD	Median	Min	Max	Change From Base n	Mean	SD	Media
(... TT group continuing)											
Treatment: All TCZ (N = 112)											
	WEEK 60	4	56.75	33.014	54.45	19.80	98.30	0			
	WEEK 62	12	75.60	36.172	68.65	17.90	158.00	0			
	WEEK 64	63	69.19	31.119	73.10	9.88	166.00	3	-69.34	148.858	-60.1
	WEEK 66	14	63.40	39.336	63.75	0.10	145.00	0			
	WEEK 68	2	58.40	3.253	58.40	56.10	60.70	0			
	WEEK 70	1	81.30		81.30	81.30	81.30	1	75.08		75.0
	WEEK 72	1	45.10		45.10	45.10	45.10	0			
	WEEK 74	3	72.17	44.310	71.10	28.40	117.00	0			
	WEEK 76	12	56.20	33.065	58.30	1.48	114.00	0			
	WEEK 78	70	72.27	39.844	71.85	0.41	269.00	3	-97.77	107.729	-117.3
	WEEK 80	2	62.55	8.415	62.55	56.60	68.50	0			
	WEEK 84	1	61.70		61.70	61.70	61.70	0			
	WEEK 86	3	79.97	19.105	69.90	68.00	102.00	0			
	WEEK 88	9	61.62	34.152	54.10	18.40	119.00	0			
	WEEK 90	54	70.48	43.393	66.90	0.13	262.00	2	-163.25	129.754	-163.2
	WEEK 92	12	67.66	18.354	66.05	39.60	97.50	0			
	WEEK 94	2	48.45	11.809	48.45	40.10	56.80	0			
	WEEK 96	1	33.60		33.60	33.60	33.60	1	27.38		27.3
	WEEK 98	1	78.70		78.70	78.70	78.70	0			
	WEEK 100	3	51.57	40.771	31.30	24.90	98.50	0			
	WEEK 102	9	62.29	39.297	58.40	12.00	131.00	0			
	WEEK 104	57	67.33	36.950	73.20	0.50	138.00	3	-87.70	172.998	-67.3

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LB10 06OCT2011:11:57:04

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIKOLAY P NIKOLOV
09/12/2018

SALLY M SEYMOUR
09/12/2018