CLINICAL PHARMACOLOGY REVIEW

BLA	125276, supplement 22
Submission Date:	10/15/2010
Brand Name	ACTEMRA®
Submission Type	Pediatric Efficacy Supplement
Generic Name	Tocilizumab (RO4877533 or myeloma receptor antibody), recombinant humanized anti-human monoclonal antibody
OCP Reviewer	Partha Roy, Ph.D.
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OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Pulmonary, Allergy and Rheumatology Products (DPARP)
Sponsor	Genentech
Formulation; Strength(s); Administration Route	Single-use vial of concentrated solution of 20 mg/mL; Intravenous infusion
Approved Indication	Indicated for Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.
Purpose of this Efficacy Supplement	To provide data to support an indication for the treatment of Systemic Juvenile Idiopathic Arthritis (sJIA) in patients 2 years and older
Proposed Dosage Regimen for the sJIA indication:	The recommended dose is 12 mg/kg for patients <30 kg and 8 mg/kg for patients ≥30 kg once every 2 weeks

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1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Tocilizumab (RO4877533, TCZ), also referred to as myeloma receptor antibody (MRA), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G_1 (IgG_1) sub-class directed against the soluble and membrane-bound interleukin 6 receptor (IL-6R). Currently, TCZ (Actemra®, 4 mg/kg with an increase to 8 mg/kg based upon clinical response) is approved in the US for RA patients who have had an inadequate response to TNF antagonist therapies. This is a pediatric supplement to add the indication of systemic onset juvenile idiopathic arthritis (sJIA) to the current tocilizumab label for the treatment of active sJIA in patients aged 2 years of age and older. TCZ is presently approved in Japan and India for sJIA and there are no other approved medicinal products globally to treat both the systemic features and the arthritis associated with sJIA.

The clinical data pivotal to the current application is derived from a three-part 5-year Phase III study (WA18221). Specifically, the application includes: 1) WA18221-Part 1: 12-week efficacy and safety study of TCZ (12 mg/kg dose for patients with body weight <30 kg and 8 mg/kg dose for patients with body weight ≥30 kg) in sJIA patients (n=112); 2) Cut of WA18221 data (cut-off date: 10th May 2010) when 50 patients reach one year in Part II of WA18221; 3) additional supportive safety and efficacy data from Japanese sJIA trials containing data for at least 56 patients through to one year.

The clinical pharmacology program included PK and PD data and PK-PD relationships from the following studies: Roche's pivotal study WA18221 and five supportive Chugai studies (LRO320, MRA011JP, MRA316JP, MRA317JP, and MRA324JP). In addition, two population PK analyses were also submitted: 1) development of alternative dosing regimen recommendations for pediatric patients with sJIA and low body weight and 2) Verification of the alternative dosing regimen recommendation using data from study WA18221.

Dose Selection

The dosing regimen is primarily selected based on pharmacokinetic analysis of data from sJIA patients (MRA316JP- Japanese Pediatric). It was observed that after 6 weeks of treatment with TCZ 8 mg/kg every 2 weeks, the proportion of patients who reached the ACR50 response was lower in patients < 30 kg (83%) than in patients weighing ≥ 30 kg (100%). Similarly, the proportion of patients who reached ACR70 was also lower in patients < 30 kg (63%) than in patients ≥ 30 kg (85%). This difference was explained by the visible trend toward lower systemic exposure to TCZ in patients with lower BW. To compensate for that, the sponsor contemplated a higher dose for the patients with lower BW (<30 kg). Therefore, a population PK modeling and simulation was performed using pooled PK data from Chugai studies MRA316JP and LRO320, with the goal to explore an alternative dosing regimen to achieve uniform exposure across the entire BW range. The post-hoc estimates of systemic exposures of TCZ using final population PK model predicted that the 12 mg/kg dose in

patients < 30 kg would yield similar systemic TCZ exposure as the patients ≥ 30 kg. With this knowledge gained from the modeling and simulation exercise, the sponsor evaluated TCZ 8 mg/kg (patients ≥ 30 kg) and 12 mg/kg (patients < 30 kg) every 2 weeks in the pivotal study WA18221. Indeed, the dosing regimen, 8 mg/kg for patients with BW ≥ 30 kg and 12 mg/kg for patients weighing < 30 kg, in study WA18221, resulted in similar serum concentrations at sampling time points over time (Figure 1) and similar systemic exposure (Table 1) between the BW categories (< 30 kg and ≥ 30 kg). Additionally, 94.7% and 75.5% of patients achieved the primary efficacy endpoint of JIA ACR30 response and absence of fever at Week 12 (ITT population) for 12 mg/kg (<30 kg bodyweight) and 8 mg/kg (≥ 30 kg bodyweight) dosing, respectively compared to only 24.3% in the placebo group. (refer to Pharmacometric Review in Appendix).

Figure 1. Tocilizumab serum concentrations (Mean ± SD) in sJIA patients with BW <30 kg (12 mg/kg) and ≥30 kg (8 mg/kg) in study WA18221.

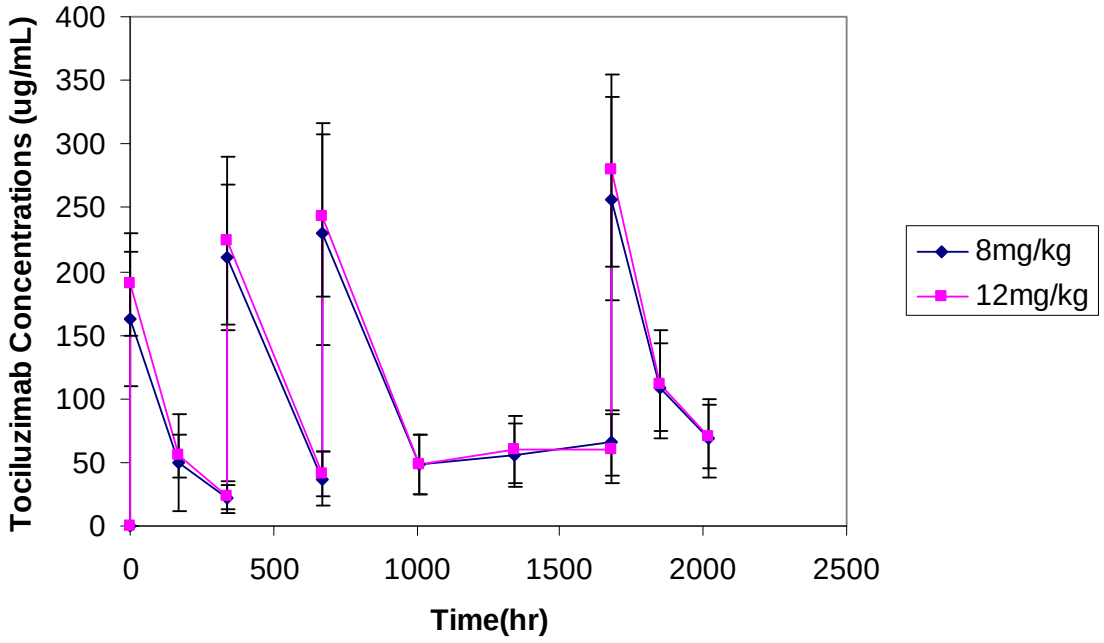


Table 1. Summary of model-predicted TCZ PK measures at week 12 by dosing groups

Parameter		8 mg/kg n = 37	12 mg/kg n = 38	All patients N= 75
C_{max}, µg/mL	Mean ±SD	226 ±54.5	263 ±54.1	245 ±57.2
	CV%	24.1	20.6	23.3
C_{min}, µg/mL	Mean ±SD	54.5 ±20.7	60.5 ±25.5	57.5 ±23.3
	CV%	38.0	42.1	40.5
$AUC_{2\ weeks}$, µg·Day/mL	Mean ±SD	1337 ±409	1346 ±426	1341 ±415
	CV%	30.5	31.6	30.9

Pharmacodynamic Findings: Inflammatory pharmacodynamic markers such as C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Acute phase serum amyloid A (SAA) were monitored in study

WA18221 while IL-6 and sIL-6R, directly linked to the mechanism of action of tocilizumab, were also measured. Following administration of TCZ, a rapid decline in mean CRP, ESR, and SAA was observed in the two dose groups (8 mg/kg and 12 mg/kg) with significant decreases seen by Week 2 and remaining suppressed through 12 weeks of treatment with tocilizumab.

Following administration of tocilizumab, IL-6 levels initially increased rapidly and then generally decreased with time, although mean concentrations did not reach baseline levels by Week 12 in either dose group. Mean sIL-6R increased rapidly by Week 2 and continued to increase toward a plateau. The observed changes in IL-6 and sIL-6R were similar between dose groups. These changes were not observed in patients receiving placebo.

The changes of inflammatory markers (CRP, ESR, and SAA) and markers of the TCZ mechanism of action (IL-6 and sIL-6R) were similar between two dose groups providing support for the proposed BW based dosing regimen in this pediatric patient population. In addition, there was no appreciable relationship between TCZ trough concentrations and PD markers tested as PD responses are generally complete at the range of steady-state clinical concentrations of TCZ in both dose groups.

Exposure-Response Evaluation
There was no clear trend towards higher systemic exposures (AUC2weeks, Cmin, and Cmax) in efficacy responders compared to non-responders. There was also no clear difference in mean PK exposures across responders for ACR30, 50, 70, and 90 responses. There were a similar proportion of patients (83-89%) within each exposure quartile who achieved the primary endpoint, ACR30 response and absence of fever at week 12. This indicates a lack of correlation between systemic exposure and efficacy response within the range of exposure achieved in the study. However, this data should be interpreted with caution for couple of reasons: 1) only a narrow exposure range was evaluated, and 2) there were a limited number of subjects in each systemic exposure quartile. However, it can be reasonably concluded that the range of systemic exposure estimated in the patient population following TCZ administration was sufficient to achieve the desired efficacy for the indication.

Similar to efficacy evaluation above, the sponsor conducted exposure-response analysis with safety by evaluating adverse events across systemic exposure (AUC_{2weeks}) quartiles. There was no trend towards increased incidence in Adverse Events (AEs) or Serious Adverse Events (SAEs) with increasing TCZ exposure, however, it should be noted that there are only small number of subjects in each exposure quartile to draw definitive conclusions.

Immunogenicity:
In study WA18221, patients were tested for anti-TCZ antibodies according to the standard testing paradigm that started with an initial screening assay and if positive followed by the confirmatory assay. If patient samples were positive for the confirmatory assay, the samples were further tested for neutralizing antibodies. All patients (N = 112) were tested at baseline and Week 12 for anti-TCZ antibodies.

All patients with assay results were negative at baseline for both confirmative and neutralizing assays. Although from a small database of TCZ treated patients (n=72), two patients (#1664 and #1005) with assay results were positive for both confirmation assay as well as neutralizing assay at week 12. Both patients discontinued from study treatment at or immediately after the week 8 infusion due to SAEs.

In Part I of study WA18221, patient 1664 had positive anti-TCZ antibody for the confirmation and the neutralizing assay. The model-predicted systemic exposure of this patient appeared to be lower than the mean values for all patients. In Part II, patient 1005 at Weeks 12 and 20 had positive anti-TCZ antibody for neutralizing assay. Since patient 1005 did not receive a full dose of 12 mg/kg TCZ at Weeks 4 and 6 due to infusion like reaction, it is not clear whether the pre-dose TCZ concentrations measured as BLQ are due to the formation anti-TCZ neutralizing antibody and/or insufficient doses received.

None of patients who missed consecutive infusions were positive for anti-TCZ antibodies after restarting dosing. None of patients with JIA ACR50 response withdrew due to loss of efficacy. Four patients, 2 from the TCZ 8 mg/kg group and 2 from the TCZ 12 mg/kg group, prematurely discontinued study treatment for lack of efficacy. None of these patients had a positive anti-TCZ neutralizing assay.

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Chemistry and Physico-Chemical Properties: Tocilizumab (RO4877533) is a humanized anti-human IL-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass produced using recombinant DNA technology.

The 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 for TCZ is $C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$ (polypeptide moiety only).

TCZ has a molecular weight of approximately 149 kDa (b) (4)

Formulation: Tocilizumab is supplied as a sterile liquid concentrate for solution for intravenous (iv) infusion available at a concentration of 20 mg/mL.

2.1.2 What are the approved therapeutic indication, dosage and route of administration?

Indication: ACTEMRA® (tocilizumab) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

ACTEMRA can be used as monotherapy or concomitantly with methotrexate or other DMARDs.

Dosage and Route of Administration: When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response.

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical trials used to support the proposed claims?

This pediatric development program consists of one 3-part 5-year pivotal Phase 3 trial (WA18221) and additional supportive Phase 2 and Phase 3 studies from Japanese development for the same indication, as described below.

1. Clinical Study Report for WA18221-Part I — consisting of a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of tocilizumab (12 mg/kg < 30 kg and 8 mg/kg ≥ 30 kg) in patients (n=112) with active sJIA;
2. Cut of WA18221 data (cut-off point: May 10, 2010) when 50 patients reach one year in Part II;

3. Additional supportive data (safety and dose-finding information) from Chugai's (Japanese) long-term sJIA studies (Table 2)

Table 2. Summary of supportive clinical studies for TCZ in sJIA

Study # Phase Location	Study Design	Treatment Dose/Regimen	Duration	Study Status No. of Patients Age range
LRO320 **Phase II** **EU**	Multi-center, open-label, single dose, cohort dose escalation	TCZ: 2, 4, or 8 mg/kg, 6 pts per cohort (3/ age group) Two age groups 2-5Y/O, 6-18 Y/O per dose level	Single dose	18 completed 18 dosed 0 withdrawn Ages 2 - 17 yrs
MRA011JP **Phase II** **Japan**	Single-center, open-label, intra-patient dose escalation/ titration study with extension phase	TCZ: 2 mg/kg q2wks x 3, then dose adjustment based on objective to normalize CRP response; 4 mg/kg q2wks, 8 mg/kg q2wks	6-14 wks (dose escalation) followed by > 1-year extension phase	10 completed 11 dosed 1 withdrawn Ages 3 - 18 yrs
MRA316JP **Phase III** **Japan**	Multi-center, double-blind, randomized, placebo-controlled, withdrawal study	TCZ: 8 mg/kg q2wks x 3 (open phase) followed by 8 mg/kg or placebo q2wks x 6 (double-blind withdrawal phase)	6 wks followed by 12 wk DB withdrawal phase	50 completed 56 dosed 6 withdrawn Ages 2 - 19 yrs
MRA317JP **Phase III Long Term Extension** **Japan**	Multi-center, open-label extension for MRA011JP and MRA316JP	TCZ 8 mg/kg q2wks	Study continued until commercially available in Japan ~5 years	56 completed 60 dosed (10 from MRA011JP and 50 from MRA316JP) 2 withdrawn
MRA324JP **Phase III** **Expanded Access Program** **Japan**	Multi-center, open-label, expanded access study (refractory sJIA pts)	TCZ 8 mg/kg q2wks, dosing interval can be shortened to 1 week	Study continued until commercially available in Japan ~2 years	74 completed 82 dosed Ages 2 - 34 yrs including 11 pts with ≥20 years of age 8 withdrawn

In addition, data from two population PK analyses are provided:

1. Development of alternative dosing regimen recommendations for pediatric patients with sJIA and low body weight.
2. Population PK analysis of study WA18221: Verification of an alternative dosing regimen recommendation for pediatric patients with sJIA and low body weight.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Concentrations of TCZ were determined in human serum samples with validated sandwich enzyme immunoassay (EIA), which was the same assay used for determining plasma levels in the original submission.

For complete review of the assay validation, refer to the Clinical Pharmacology Review by Dr. Lei Zhang dated 08/21/2008 for the original BLA submission (BLA 125276).

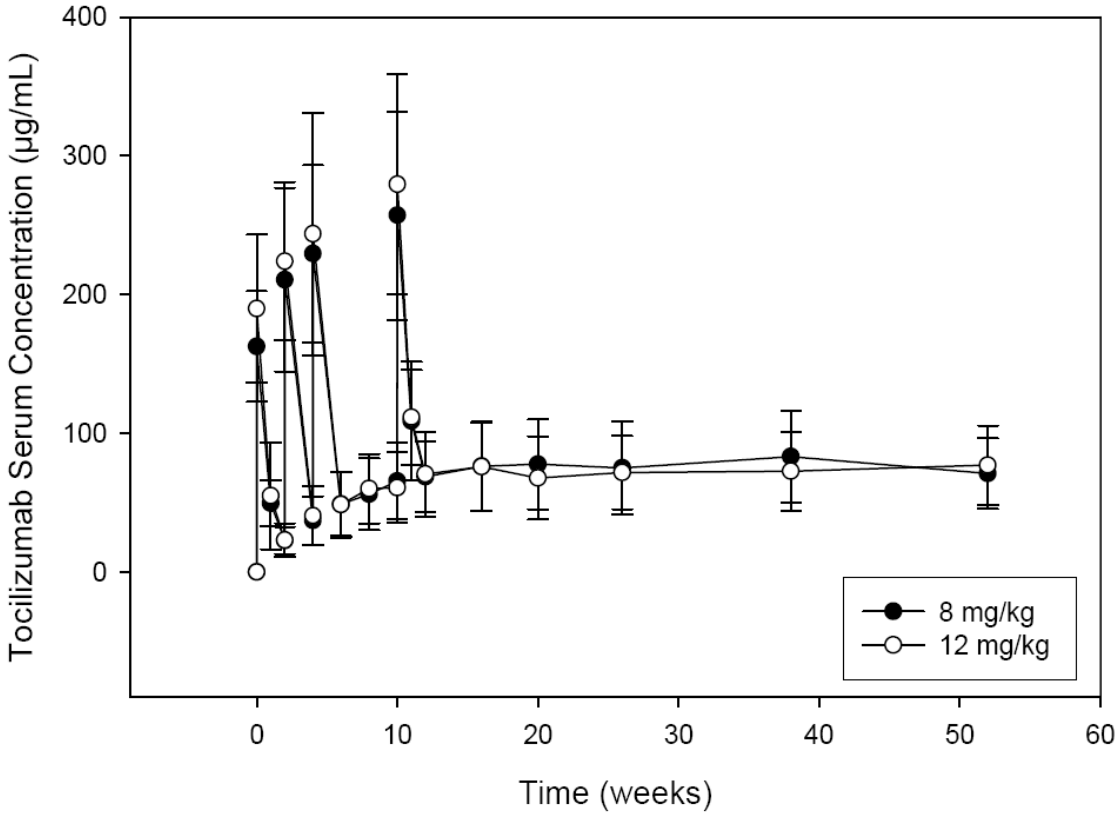
2.2.3 What was the rationale for the dose and dosing regimen of TCZ in sJIA patients?

The sponsor provided rationale for dosing based on efficacy response and systemic exposure data they collected in the early studies. Initially, the dose was selected based on biomarker response (C-reactive protein) as well as achieving and maintaining a minimum serum TCZ concentration. The rationale for dosing every 2 weeks came from the observation that clearance of TCZ appeared higher in sJIA patients compared to adults where the dosing is once every 4 weeks. The rationale for dosing 12 mg/kg in patients with body weight <30 kg and 8 mg/kg in patients with bodyweight ≥30 kg was based on achieving uniform exposure between the two bodyweight groups. Following 8 mg/kg dose of TCZ, the lower bodyweight children reported lower clinical response compared to children with bodyweights ≥30 kg. Detailed analysis and justification of dose and dosing regimen selection can be found in the Pharmacometric Review by Dr. Atul Bhattaram attached with this review (Appendix).

2.2.4 What are the PK characteristics of TCZ in sJIA pediatric patients, particularly after long-term treatment with Actemra administered once every 2 weeks?

The mean (± SD) pre-dose concentration-time profile of TCZ by treatment group up to Week 52 of treatment in study WA18221 is illustrated in Figure 2.

Figure 2. Observed Mean (±SD) pre-dose serum TCZ concentration time profile by treatment group (8 and 12 mg/kg) from baseline to week 52 (study WA18221)



Following TCZ administration, mean TCZ pre-dose concentrations trended upwards over time until Week 10 and stabilized after Week 12 in both treatments (Figure 2), indicating that steady-state has been reached consistent with the half-life of 18-23 days. Pre-dose concentrations remained stable between Weeks 12 to 52 with observed serum TCZ concentrations of 69.5±27.7 and 73.8±26.9 µg/mL, respectively. Comparing TCZ serum concentrations between the two treatment groups, 8 mg/kg and 12 mg/kg, revealed similar serum concentrations at all sampling points over time through Week 52 (Figure 2).

Besides collecting sparse PK samples from study WA18221, the sponsor submitted two population PK analyses to support dose and dosing regimen and also to evaluate the influence of various covariates on the PK parameters. The detailed review of the population PK modeling and analyses is captured in the Pharmacometric Review by Dr. Atul Bhattaram (Appendix).

The posthoc estimated PK exposures by treatment group are summarized in Table 3. Mean computed PK exposures (AUC_{2weeks}, C_{max} and C_{min}) were similar between the two treatment groups (8 mg/kg for body weight ≥ 30 kg and 12 mg/kg for bodyweight <30 kg).

Table 3. Summary of predicted TCZ PK exposures at week 12 by treatment group (Study WA18221)

Parameter		8 mg/kg N= 37	12 mg/kg N= 38	All patients N= 75
C_{max}, µg/mL	Mean ±SD	226 ±54.5	263 ±54.1	245 ±57.2
	CV%	24.1	20.6	23.3
C_{min}, µg/mL	Mean ±SD	54.5 ±20.7	60.5 ±25.5	57.5 ±23.3
	CV%	38.0	42.1	40.5
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD	1337 ±409	1346 ±426	1341 ±415
	CV%	30.5	31.6	30.9

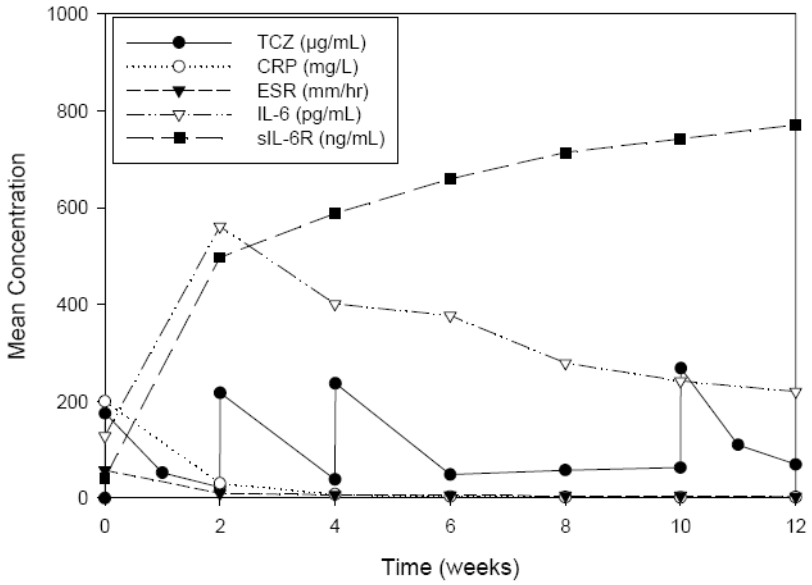
Using population PK analyses, the total clearance of TCZ was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance estimated in population PK analysis was 0.17 L/day (or 7.1 mL/hour) in sJIA pediatric patients. In sJIA patients, the volume of distribution at steady state is estimated to be 2.54 L. The half-life of TCZ is concentration dependent and is estimated to range from 18.4 to 22.7 days for 8 mg/kg (body weight ≥ 30 kg) and 19.2 to 23 days for 12 mg/kg (body weight < 30 kg) treatment groups at week 12.

2.2.5. What pharmacodynamic markers were evaluated?

Following administration of TCZ, a rapid decline in mean markers of inflammation (CRP, ESR and SAA) was observed across all studies. CRP concentration normalized or decreased dramatically after TCZ dosing and remained within reference ranges through 12 weeks of treatment with TCZ (Figure 3 below). Similarly with ESR and SAA, rapid decreases in mean levels were observed following administration of TCZ with declines observed by 2 weeks and remaining suppressed through 12 weeks of treatment with TCZ. The changes of CRP, ESR and SAA are comparable between the 8 mg/kg and 12 mg/kg treatment groups.

As shown in Figure 3, after TCZ administration, mechanistic markers such as IL-6 and sIL-6R increased rapidly upon administration of TCZ with IL-6 subsequently declining gradually trending towards baseline while sIL-6R continued to increase, approaching a plateau through week 12 when steady-state systemic exposure of TCZ is attained.

Figure 3. Relationship of TCZ PK and mean PD markers in all patients who received TCZ treatment in study WA18221.



2.2.6. What was exposure-response relationship of tocilizumab in terms of efficacy and safety?

There was no clear trend toward higher PK exposures (AUC_{2weeks}, $C_{min,}$ and C_{max}) in responders compared to non-responders. There was also no clear difference in mean PK exposures across responders for ACR30, 50, 70, and 90 responses (Table 4). One of the difficulties in making a definite conclusion about this is the fact that there were limited number of subjects in the non-responder group although one can argue that consistently, exposure in responders, on average, are numerically greater (5-20%) than non-responders. Also important to note is that there is a similar proportion of patients within each exposure quartile who achieved the primary endpoint, ACR30 response and absence of fever at week 12 (Table 5). Again, there are only limited number of patients in each quartile to draw a definitive conclusion. However, these data collectively indicate lack of correlation between TCZ systemic exposure and efficacy endpoints, suggesting that even the lowest systemic exposure within the range of exposures (Table 3 above) in the sJIA patient population was sufficient to achieve the desired efficacy. Refer to the Pharmacometric Review for further analyses of the exposure-response relationship for efficacy.

Table 4. Summary of TCZ PK exposures at week 12 by ACR response status for all patients

RESPONDERS					
Parameter		**JIA ACR30 N=68**	**JIA ACR50 N=64**	**JIA ACR70 N=53**	**JIA ACR90 N=28**
C_{max}, µg/mL	Mean ±SD	249 ±55.8	249 ±56.9	254 ±54.0	255 ±43.1
	CV%	22.4	22.9	21.3	16.9
C_{min}, µg/mL	Mean ±SD	59.0 ±23.4	59.6 ±23.9	61.4 ±22.1	61.0 ±20.0
	CV%	39.7	40.1	36.0	32.8
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD	1363 ±411	1373 ±421	1401 ±378	1386 ±345
	CV%	30.2	30.7	27.0	24.9
NON-RESPONDERS					
Parameter		**JIA ACR30 N=7**	**JIA ACR50 N=11**	**JIA ACR70 N=22**	**JIA ACR90 N=47**
C_{max}, µg/mL	Mean ±SD	205 ±59.2	218 ±53.8	223 ±60.0	239 ±64.0
	CV%	28.9	24.7	27.0	26.8
C_{min}, µg/mL	Mean ±SD	44.2 ±19.5	45.2 ±15.8	48.2 ±24.1	55.6 ±25.3
	CV%	44.1	35.0	50.0	45.5
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD	1133 ±417	1158 ±334	1197 ±470	1315 ±452
	CV%	36.8	28.8	39.3	34.4

Table 5. Summary of Percentage of Patients Achieving JIA ACR30 and Absence of Fever Response Status at Week 12 by Exposure Quartiles

Parameter		**Q1**	**Q2**	**Q3**	**Q4**
C_{max}	N	19	19	19	18
	Responders (%)	15 (78.9)	17 (89.5)	16 (84.2)	16 (88.9)
C_{min}	N	19	19	19	18
	Responders (%)	16 (84.2)	17 (89.5)	15 (78.9)	16 (88.9)
$AUC_{2\ weeks}$	N	19	19	19	18
	Responders (%)	16 (84.2)	17 (89.5)	16 (84.2)	15 (83.3)

Note: Mean AUC_{2weeks} (µg.day/mL) for Q1: 849, Q2: 1178, Q3: 1445, Q4: 1925

Similar to efficacy evaluation above, the sponsor conducted exposure-response analysis with safety by evaluating adverse events across systemic exposure (AUC_{2weeks}) quartiles. There was no trend towards increased incidence in Adverse Events (AEs) with increasing TCZ exposure (Table 6). Similar conclusion can be drawn for serious adverse events (SAEs) where most SAEs occurred in patients in the first exposure quartile (Q1). It should be noted that there are only small number of subjects in each exposure quartile to draw definitive conclusions about exposure-safety relationship.

Table 6. Summary of Percentage of patients reporting AEs by body system and preferred term to week 12 by systemic exposure quartiles

Body System/Adverse Event*	AUC_{2weeks}			
	Q1 N=19 No. (%)	Q2 N=19 No. (%)	Q3 (N=19) No. (%)	Q4 N=18 No. (%)
All Body Systems	19 (100)	16 (84.2)	17 (89.5)	14 (77.8)
Infections and Infestation	11 (57.9)	8 (42.1)	6 (31.5)	9 (50)
Gastrointestinal disorders	3 (15.8)	5 (26.3)	2 (10.5)	4 (22.2)
Skin and Subcutaneous Tissue disorders	4 (21.1)	1 (5.3)	3 (15.8)	4 (22.2)
Nervous System disorders	3 (15.8)	1 (5.3)	2 (10.5)	2 (11.1)
Respiratory, Thoracic, and Mediastinal disorders	3 (15.8)	1 (5.3)	2 (10.5)	1 (5.6)
	C_{max}			
	Q1	Q2	Q3	Q4
All Body Systems	18 (94.7)	16 (84.2)	18(94.7)	14 (77.8)
Infections and Infestation	9 (47.4)	6 (31.6)	10 (52.6)	9 (50)
Gastrointestinal disorders	2 (10.5)	2 (10.5)	8 (42.1)	2 (11.1)
Skin and Subcutaneous Tissue disorders	4 (21.1)	2 (10.5)	2 (10.5)	4 (22.2)
Nervous System disorders	2 (10.5)	2 (10.5)	3 (15.8)	1 (5.6)
Respiratory, Thoracic, and Mediastinal disorders	2 (10.5)	2 (10.5)	2 (10.5)	1 (5.6)
	C_{min}			
	Q1	Q2	Q3	Q4
All Body Systems	19 (100)	16 (84.2)	16 (84.2)	15 (83.3)
Infections and Infestation	10 (52.6)	9 (47.4)	6 (31.6)	9 (50.0)
Gastrointestinal disorders	2 (10.5)	5 (26.3)	3 (15.8)	4 (22.2)
Skin and Subcutaneous Tissue disorders	3 (15.8)	2 (10.5)	3 (15.8)	4 (22.2)
Nervous System disorders	2 (10.5)	2 (10.5)	2 (10.5)	2 (11.1)
Respiratory, Thoracic, and Mediastinal disorders	3 (15.8)	1 (5.3)	2 (10.5)	1 (5.6)

* Total patients with at least one AE; Only most frequent AEs are listed. Details can be found in source data.
Q1, Q2, Q3 and Q4 are the first (0- < 25%), second (> 25 to < 50%), third (>50 to < 75%) and fourth (> 75 – 100%) quartiles of individual exposure parameters as listed.

2.3 **Intrinsic Factors**

2.3.1. Is there any effect of 1) age, 2) gender and 3) race on the pharmacokinetics of TCZ in the sJIA patient population?

Nonlinear mixed effects modeling was used to analyze the serum TCZ concentration-time data collected over 12 weeks of treatment (see Appendix for the Pharmacometric Report). Systemic exposure (AUC_{2weeks}, C_{max} and C_{min} at Week 12), was estimated for all patients who had provided samples.

A summary of estimated systemic exposures (AUC2weeks, Cmin and Cmax) of TCZ at Week 12 by age category is provided in Table 7. Mean PK exposures were similar among age categories (2-5 yrs, 6-12 yrs, and 13-18 yrs), indicating lack of age effect on the pharmacokinetics of TCZ across the entire pediatric age range 2 years and above.

Table 7. Mean PK parameters at week 12 by age categories across the pediatric age range

Parameter		2-5 yrs N=16	6-12 yrs N=33	13-18 yrs N=26
C_{max}, µg/mL	Mean ±SD	272 ±56.7	240 ±59.1	234 ±51.5
	CV%	20.8	24.6	22.0
C_{min}, µg/mL	Mean ±SD	57.2 ±27.9	56.3 ±24.4	59.3 ±19.5
	CV%	48.8	43.3	32.9
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD	1240 ±450	1313 ±412	1439 ±391
	CV%	36.2	31.4	27.2

Model-independent PK parameters in Japanese pediatric sJIA patients and Japanese adult RA patients are compared in Table 8. BW-normalized clearance of TCZ was higher in sJIA patients (0.78 ± 0.34 mL/kg in Group 1 and 0.89 ± 0.18 mL/kg in Group 2) than in adult RA patients (0.16 ± 0.12 mL/kg) at 8 mg/kg.

Table 8. Mean PK Parameters of TCZ after Single Infusion of 8 mg/kg to sJIA pediatric vs. adult RA patients

Study	Population	AUC_{inf}, mg·hr/mL	$T_{1/2}$, hr	CL, mL/kg
LRO320	sJIA-Group 1 (2-5 yr), N=3	11.6 ± 4.5	104 ±52	0.78 ± 0.34
	sJIA-Group 2 (16-18 yr), N=3	9.2 ± 1.7	92 ± 28	0.89 ± 0.18
LRO301	Japanese Adult RA, N=25	31.2 ± 7.7	133 ± 23	0.16 ± 0.12

Population PK analyses confirmed the findings of greater clearance in pediatric sJIA patients. Following 8 mg/kg IV infusion (once every 2 weeks in children compared to once every 4 weeks in adults), the C_{min} is 6-fold higher in sJIA patients than in adult RA patients (54.5 µg/mL vs 8.6 µg/mL), and AUC_{2weeks} in sJIA patients is similar to AUC4weesk in adult RA patients (1337 µg/mL vs 1417 µg·day/mL).

Estimated TCZ systemic exposures (AUC_{2weeks}, C_{min} and C_{max}) at week 12 by gender is provided in Table 9. Mean PK exposures were similar between males and females, indicating no effect of gender on pharmacokinetics of TCZ.

Table 9. Mean PK parameters at week 12 by gender in the sJIA patient population

Parameter		Female N=39	Male N=36
C_{max}, µg/mL	Mean ±SD	243 ±59.0	246 ±55.8
	CV%	24.3	22.7
C_{min}, µg/mL	Mean ±SD	57.1 ±24.2	58.0 ±22.7
	CV%	42.3	39.1
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD	1312 ±405	1373 ±428
	CV%	30.9	31.1

Apart from the PK data from study WA18221, early trials (LRO320 and MRA316JP) also reported PK parameters based on non-compartmental analysis of rich PK data. PK parameters from WA18221 are not compared directly to PK parameters from the earlier studies due to different treatment durations. However,

Cmin at Week 18 in study MRA316JP (56.7 ±18.8 μg/mL) is comparable to the Cmin at Week 12 in study WA18221 (54.5 ±20.7 μg/mL) following 8 mg/kg every 2 weeks dosing, indicating that PK is comparable between Japanese and Caucasian populations. The population PK parameters from WA18221 (predominately Caucasian) were also found to be similar to the PK parameters from MRA316JP (Japanese sJIA patients). These observations indicate that PK is similar between Caucasian and Japanese populations, therefore no apparent effect of race on TCZ PK in these populations of sJIA patients.

2.3.2. What were the immunogenicity findings for tocilizumab? What was the impact of immunogenicity on exposure and/or safety and efficacy?

In study WA18221, patients were tested for anti-TCZ antibodies according to the standard testing paradigm that started with an initial screening assay and if positive followed by the confirmatory assay. If patient samples were positive for the confirmatory assay, the samples were further tested for neutralizing antibodies. All patients (N = 112) were tested at baseline and Week 12 for anti-TCZ antibodies.

All patients with assay results were negative at baseline for both confirmative and neutralizing assays. Although from a small database of TCZ treated patients (n=72), only two patients (#1664 and #1005) with assay results were positive for both confirmation assay as well as neutralizing assay at week 12. Both patients discontinued from study treatment at or immediately after the week 8 infusion due to SAEs. The last treatment of TCZ 12 mg/kg for patient# 1664 was 60% of the dose at Week 8 and then dropped out of the study due to the occurrence of SAE of angioedema. The model predicted AUC_{2weeks} and C_{min} exposure of patient# 1664 at Week 12 (844 μg · day/mL and 31.6 μg/mL, respectively) appeared to be lower than the mean values for all patients (1341 μg · day/mL and 57.5 μg/mL, respectively). The model predicted Cmax at Week 12 was 265 μg/mL which was comparable to the mean Cmax for all patients (245 μg/mL).

Patient 1005 had reported positive results for confirmatory as well as neutralizing assay at Week 12 and Week 20. This patient was randomized at baseline to placebo treatment and then escaped to open-label TCZ 12 mg/kg at Week 2. The patient received a complete dose at Week 2 without issue, but only received 12% of the dose at Week 4 and 78% at Week 6 due to infusion-like reactions. After pre-medication and a slowed infusion rate, the patient received a complete dose at Week 8. The patient was discontinued from treatment following Week 8 due to macrophage activating syndrome. As patient #1005 was originally randomized to placebo, model-predicted PK parameters were not estimated. This patient's observed serum TCZ levels were BLQ at all sampling points taken (excluding one post dose sample at Week 2 immediately after completion of the infusion). Since patient 1005 did not receive a full dose of 12 mg/kg at Weeks 4 and 6, it is not clear whether the pre-dose TCZ concentration of below the limit of detection is due to the formation of anti-TCZ antibody and/or insufficient doses received.

None of patients who missed consecutive infusions were positive for anti-TCZ antibodies after restarting dosing. None of patients with JIA ACR50 response withdrew due to loss of efficacy. Four patients, 2 from the TCZ 8 mg/kg group and 2 from the TCZ 12 mg/kg group, prematurely discontinued study treatment for lack of efficacy. None of these patients had a positive anti-TCZ neutralizing assay.

3 Preliminary Labeling Recommendation

1. Under section 6.1 Clinical Trials Experience

(b) (4)

4 Appendix

4.1 **Pharmacometric Review**

APPEARS THIS WAY ON ORIGINAL

Office of Clinical Pharmacology:
Pharmacometric review

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 Did the sponsor provide rationale for the dose and dosing regimen of tocilizumab (TCZ) in patients with sJIA?

Yes, the sponsor conducted studies that provided rationale for choice of dose and dosing regimen of TCZ in patients with sJIA.

Table 1 lists the summary of early clinical studies for TCZ in sJIA. These studies provided the basis for proposed dose and dosing regimen of TCZ in the registration trial (WA18221).

Table 1. Summary of supportive clinical studies for TCZ in sJIA

Study # Phase Location	Study Design	Treatment Dose/Regimen	Duration	Study Status No. of Patients Age range
LRO320 **Phase II** **EU**	Multi-center, open-label, single dose, cohort dose escalation	TCZ: 2, 4, or 8 mg/kg, 6 pts per cohort (3/ age group) Two age groups 2-5Y/O, 6-18 Y/O per dose level	Single dose	18 completed 18 dosed 0 withdrawn Ages 2 - 17 yrs
MRA011JP **Phase II** **Japan**	Single-center, open-label, intra-patient dose escalation/ titration study with extension phase	TCZ: 2 mg/kg q2wks x 3, then dose adjustment based on objective to normalize CRP response; 4 mg/kg q2wks, 8 mg/kg q2wks	6-14 wks (dose escalation) followed by > 1-year extension phase	10 completed 11 dosed 1 withdrawn Ages 3 - 18 yrs
MRA316JP **Phase III** **Japan**	Multi-center, double-blind, randomized, placebo-controlled, withdrawal study	TCZ: 8 mg/kg q2wks x 3 (open phase) followed by 8 mg/kg or placebo q2wks x 6 (double-blind withdrawal phase)	6 wks followed by 12 wk DB withdrawal phase	50 completed 56 dosed 6 withdrawn Ages 2 - 19 yrs
MRA317JP **Phase III Long Term Extension** **Japan**	Multi-center, open-label extension for MRA011JP and MRA316JP	TCZ 8 mg/kg q2wks	Study continued until commercially available in Japan ~5 years	56 completed 60 dosed (10 from MRA011JP and 50 from MRA316JP) 2 withdrawn
MRA324JP **Phase III** **Expanded Access Program** **Japan**	Multi-center, open-label, expanded access study (refractory sJIA pts)	TCZ 8 mg/kg q2wks, dosing interval can be shortened to 1 week	Study continued until commercially available in Japan ~2 years	74 completed 82 dosed Ages 2 - 34 yrs including 11 pts with ≥20 years of age 8 withdrawn

Sponsor's Rationale for 8 mg/kg dose every 2 weeks

Patients in MRA011JP received three doses of 2 mg/kg TCZ and the dose was escalated to 4 mg/kg and 8 mg/kg as required to normalize CRP. When the serum TCZ concentration was at or above the limit of quantification (1 μg/mL) in this study, CRP

was virtually normal. Based on results from dose escalation during the course of the study to maintain TCZ at measurable levels, the TCZ dose needed to be increased to 8 mg/kg in the patients in whom an adequate serum TCZ concentration could not be maintained at 4 mg/kg. The 8 mg/kg dose was therefore proposed for the Phase III study MRA316JP in Japan.

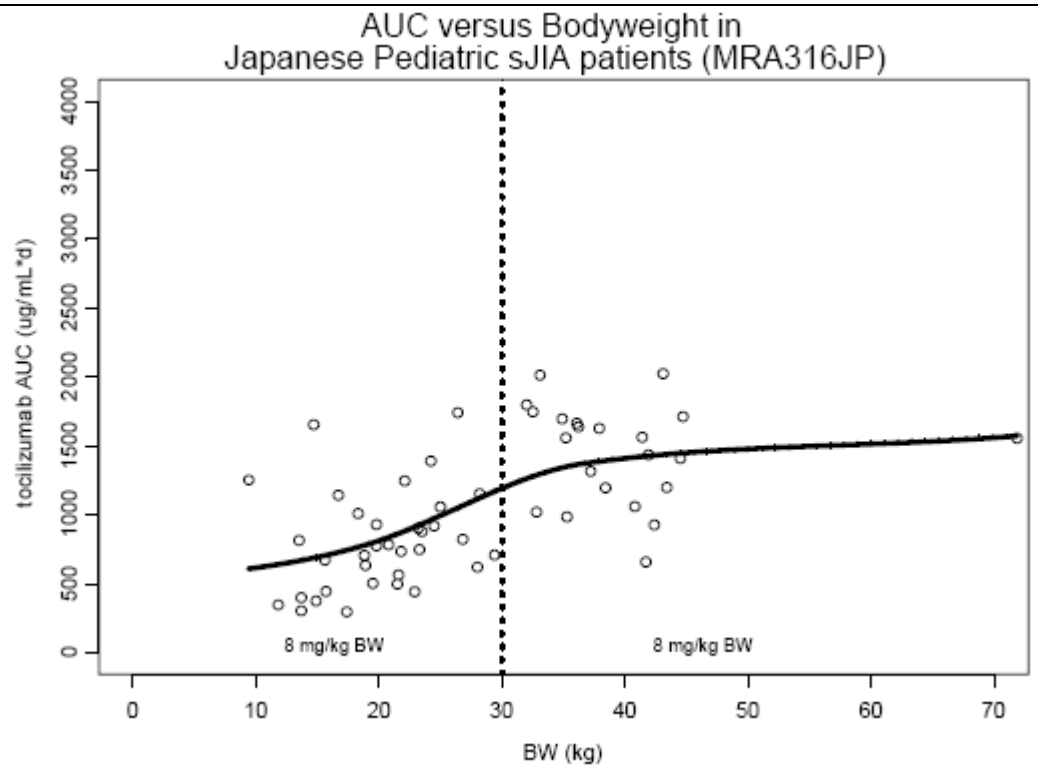
Sponsor's Rationale for every 2 weeks dosing interval

Following single dose infusions of TCZ to sJIA patients in Study LR0320, PK and PD results showed that TCZ clearance appeared higher in sJIA patients than in adult RA patients, and that serum IL-6 concentrations were also higher before and after dosing in these children than in adult RA patients. The PD response (IL-6) appeared to decline over a 4-week period following the infusion of TCZ and TCZ was undetectable in plasma by 2 weeks after dosing in the majority of patients. Thus, the TCZ dose frequency of every 2 weeks was appropriate for future studies.

Sponsor's Rationale for 8 mg/kg dose every 2 weeks in patients with body weight ≥30 kg and 12 mg/kg every 2 weeks in patients with body weight <30 kg

A Phase III study (MRA316JP) assessing the PK, efficacy, and safety of TCZ with 8 mg/kg every 2 weeks was conducted in Japanese sJIA patients. It was observed that the clinical response was lower in children with a low body weight (BW), compared to patients with a higher BW. After 6 weeks of treatment with TCZ 8 mg/kg every 2 weeks, the proportion of patients who reached the ACR50 response was lower in patients < 30 kg (83%) than in patients weighing ≥ 30 kg (100%). Similarly, the proportion of patients who reached ACR70 was also lower in patients < 30 kg (63%) than in patients ≥ 30 kg (85%). This difference was explained by the visible trend toward lower systemic exposure to TCZ in patients with lower BW (**Figure 1**).

Figure 1. Dosing with 8mg/kg results in low exposure in pediatric patients with low bodyweight



Therefore, for the registration trial (WA18221), population PK modeling and simulation was performed using pooled PK data from Chugai studies MRA316JP and LRO320, with the goal to explore an alternative dosing regimen to achieve uniform exposure across a wide BW range. The post-hoc estimates of systemic exposures of TCZ using final population PK model, clearly showed that the 12 mg/kg dose in patients < 30 kg would gain similar exposures as the patients ≥ 30 kg.

Table 2 shows the observed TCZ exposure with studied dose of 8 mg/kg and predicted TCZ exposure with the proposed dose of 12 mg/kg for study MRA316JP.

Table 2. TCZ observed **exposure with studied dose of 8 mg/kg and predicted** exposure with the proposed **dose of 12 mg/kg for study MRA316JP**

		Dose		
		BW < 30 kg (n=34)		BW ≥ 30 kg (n=22)
		8 mg/kg q2wk	12 mg/kg q2wk	8 mg/kg q2wk
AUC_{2weeks} [µg·day /mL]	Median Min-Max	761 294 - 1743	1227 471 - 2771	1556 657 - 2024
C_{max} [µg/mL]	Median Min-Max	173 81 - 292	265 124 - 449	280 189 - 364
C_{min} [µg/mL]	Median Min-Max	22 2.5 - 83	39 5.1 - 144	51 9.3 - 82

Source: Table 39 from page 93 in summary-clin-pharm.pdf

Is the proposed dosing regimen for tocilizumab (TCZ) based on body weight cut off of 30 kg acceptable?

Yes, the proposed dosing regimen for TCZ as shown in **Table 3**, based on body weight cut off of 30 kg, is acceptable if there are no major safety issues.

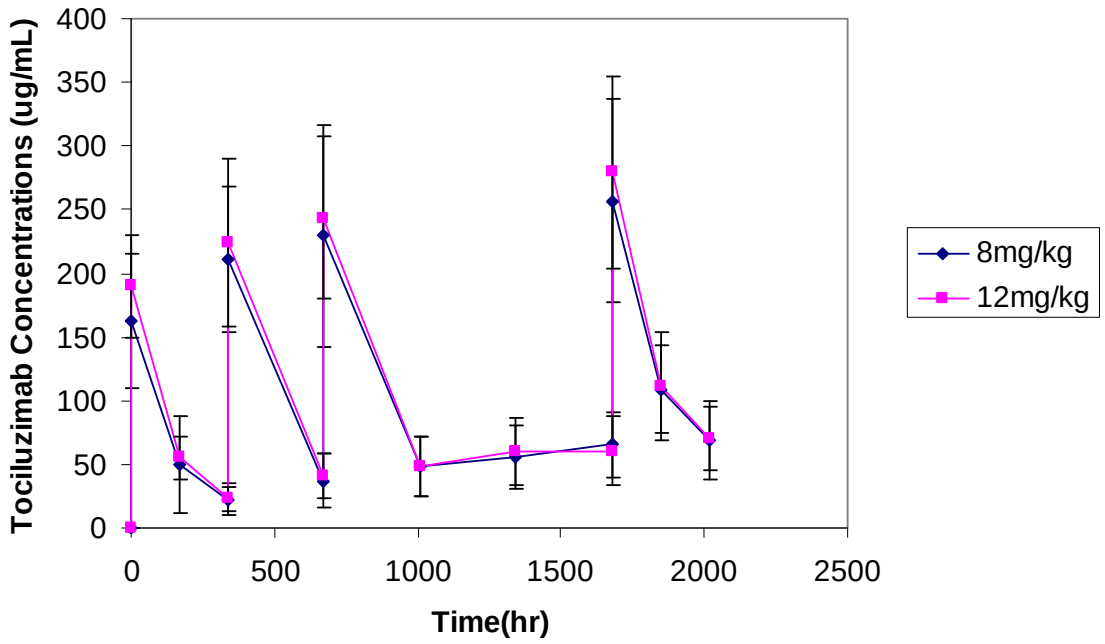
Table 3. Proposed dosing regimen for TCZ in sJIA

Recommended sJIA Dosage Every 2 Weeks	
Patients < 30 kg	12 mg/kg
Patients ≥ 30 kg	8 mg/kg

Source: Proposed drug label

Figure 2 shows that the TCZ concentrations are similar in patients with body weight <30 kg (treated with 12 mg/kg every 2 weeks) and ≥30 kg (treated with 8 mg/kg every 2 weeks) in WA18221.

Figure 2. TCZ concentrations (mean±standard deviation) in patients with body weight <30 kg (treated with 12 mg/kg every 2 weeks) and ≥30 kg (treated with 8 mg/kg every 2 weeks) in WA18221



Source: Data from Page 697-704 from wa18221.pdf report.

The predicted C_{max}, C_{min}, AUC_{2weeks} for 8 mg/kg and 12 mg/kg dose groups are shown in **Table 4**.

Table 4. Summary of predicted TCZ PK exposures at week 12 by treatment group

Parameter		8 mg/kg N= 37	12 mg/kg N= 38	All patients N= 75
C_{max}, µg/mL	Mean ±SD CV%	226 ±54.5 24.1	263 ±54.1 20.6	245 ±57.2 23.3
C_{min}, µg/mL	Mean ±SD CV%	54.5 ±20.7 38.0	60.5 ±25.5 42.1	57.5 ±23.3 40.5
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD CV%	1337 ±409 30.5	1346 ±426 31.6	1341 ±415 30.9

Source: Table 4 on Page 27 of summary-clin-pharm.pdf

Table 5 shows the percentage of patients with a JIA ACR30 response and absence of fever at Week 12 (ITT Population) in Study WA18221.

Table 5. Percentage of Patients with a JIA ACR30 Response and Absence of Fever (Primary endpoint) at Week 12 (ITT Population)

	Placebo (N=37)	Body weight <30 kg (treated with 12 mg/kg) (N=38)	Body Weight ≥30 kg (treated with 8 mg/kg) (N=37)
Percentage of Patients with a JIA ACR30 response and absence of fever at Week 12 (ITT population)	24.3	94.7	75.5

Source: Table 12 on Page 129 of WA18221.pdf

Figure 3 shows the relationship between TCZ AUC_{2weeks} and percentage of responders, non-responders based on JIA ACR30 Response,LOCF at week 12 in study WA18221.

Figure 3. Relationship between TCZ (tocilizumab) AUC_{2weeks} and percentage of responders (+), non-responders (o) based on week 12 JIA ACR30 Response, LOCF. Shown also are the number of responders, non-responders in each AUC quartile

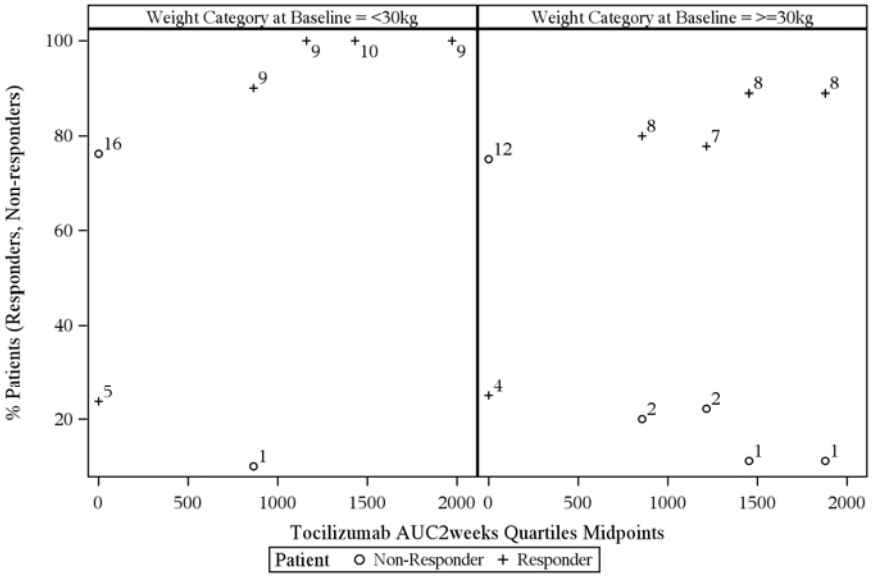


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Table shows that Cmax, Cmin, AUC_{2weeks} of TCZ are not different in responders and non-responders based on ACR response status.

Table 6. Summary of TCZ PK exposures at week 12 by ACR response status for all patients

RESPONDERS					
Parameter		**JIA ACR30 N=68**	**JIA ACR50 N=64**	**JIA ACR70 N=53**	**JIA ACR90 N=28**
C_{max}, µg/mL	Mean ±SD CV%	249 ±55.8 22.4	249 ±56.9 22.9	254 ±54.0 21.3	255 ±43.1 16.9
C_{min}, µg/mL	Mean ±SD CV%	59.0 ±23.4 39.7	59.6 ±23.9 40.1	61.4 ±22.1 36.0	61.0 ±20.0 32.8
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD CV%	1363 ±411 30.2	1373 ±421 30.7	1401 ±378 27.0	1386 ±345 24.9
NON-RESPONDERS					
Parameter		**JIA ACR30 N=7**	**JIA ACR50 N=11**	**JIA ACR70 N=22**	**JIA ACR90 N=47**
C_{max}, µg/mL	Mean ±SD CV%	205 ±59.2 28.9	218 ±53.8 24.7	223 ±60.0 27.0	239 ±64.0 26.8
C_{min}, µg/mL	Mean ±SD CV%	44.2 ±19.5 44.1	45.2 ±15.8 35.0	48.2 ±24.1 50.0	55.6 ±25.3 45.5
$AUC_{2\ weeks}$, µg·day/mL	Mean ±SD CV%	1133 ±417 36.8	1158 ±334 28.8	1197 ±470 39.3	1315 ±452 34.4

Source: Table 13 on Page 45 of summary-clin-pharm.pdf

Table 7 shows that the the percentage of patients achieving JIA ACR30 and absence of fever response status at Week 12 are similar across exposure quartiles.

Table 7. Summary of percentage of patients achieving JIA ACR30 and absence of fever response status at Week 12 by exposure quartiles

Parameter		**Q1**	**Q2**	**Q3**	**Q4**
C_{max}	N Responders (%)	19 15 (78.9)	19 17 (89.5)	19 16 (84.2)	18 16 (88.9)
C_{min}	N Responders (%)	19 16 (84.2)	19 17 (89.5)	19 15 (78.9)	18 16 (88.9)
$AUC_{2\ weeks}$	N Responders (%)	19 16 (84.2)	19 17 (89.5)	19 16 (84.2)	18 15 (83.3)

Quartiles are defined as those patients falling within 0 - ≤ 25%, >25 - ≤50%, >50 - ≤75%, >75-100% of exposures.

Source: Table 5 on Page 27 of summary-clin-pharm.pdf

Table 8 shows the summary of adverse events (AEs) with an incidence rate of ≥ 5% to Week 12 by Preferred Term and Trial Treatment (Safety Population).

Table 8. Summary of AEs with an Incidence Rate of ≥ 5% to Week 12 by Preferred Term and Trial Treatment (Safety Population)

Adverse Event	Placebo N = 37 No. (%)	TCZ 8 mg/kg N = 37 No. (%)	TCZ 12 mg/kg N = 38 No. (%)	All TCZ N = 75 No. (%)
UPPER RESPIRATORY TRACT INFECTION	4 (10.8)	4 (10.8)	6 (15.8)	10 (13.3)
HEADACHE	3 (8.1)	5 (13.5)	2 (5.3)	7 (9.3)
NASOPHARYNGITIS	1 (2.7)	2 (5.4)	6 (15.8)	8 (10.7)
DIARRHOEA	1 (2.7)	3 (8.1)	2 (5.3)	5 (6.7)
JUVENILE ARTHRITIS	5 (13.5)	-	2 (5.3)	2 (2.7)
NEUTROPENIA	1 (2.7)	1 (2.7)	2 (5.3)	3 (4.0)
OROPHARYNGEAL PAIN	1 (2.7)	2 (5.4)	1 (2.6)	3 (4.0)
ARTHROPOD BITE	-	1 (2.7)	2 (5.3)	3 (4.0)
BACK PAIN	-	1 (2.7)	2 (5.3)	3 (4.0)
GASTROENTERITIS VIRAL	-	1 (2.7)	2 (5.3)	3 (4.0)
PHARYNGITIS	2 (5.4)	1 (2.7)	1 (2.6)	2 (2.7)
PYREXIA	6 (16.2)	-	-	-
URTICARIA	-	-	3 (7.9)	3 (4.0)
VOMITING	-	2 (5.4)	1 (2.6)	3 (4.0)
COUGH	1 (2.7)	2 (5.4)	-	2 (2.7)
DIZZINESS	1 (2.7)	2 (5.4)	-	2 (2.7)
HAEMATURIA	1 (2.7)	-	2 (5.3)	2 (2.7)
ABDOMINAL PAIN	-	-	2 (5.3)	2 (2.7)
DYSMENORRHOEA	-	2 (5.4)	-	2 (2.7)
GASTROINTESTINAL DISORDER	-	2 (5.4)	-	2 (2.7)
INFLUENZA LIKE ILLNESS	2 (5.4)	1 (2.7)	-	1 (1.3)
JOINT SPRAIN	-	2 (5.4)	-	2 (2.7)

Investigator text for Adverse Events encoded using MedDRA version 12.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Source: Table 46 on Page 194 of wa18221.pdf

1.2 Recommendations

None

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Sponsor's Proposal

Section 12.3 Pharmacokinetics

(b) (4)

[redacted]

(b) (4)

2 Pertinent regulatory background

Tocilizumab (RO4877533, TCZ), also referred to as myeloma receptor antibody (MRA), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G_1 (IgG_1) sub-class directed against the soluble and membrane-bound interleukin 6 receptor (sIL-6R and mIL-6R). TCZ (Actemra®, 4 mg/kg with an increase to 8 mg/kg based upon clinical response) is approved in the US for RA patients who have had an inadequate response to anti-TNFs. sJIA is a subset of juvenile idiopathic arthritis (JIA) that is characterized by the presence of arthritis, intermittent fever, and rash and comprises between 4% and 17% of all cases of JIA. Currently, there are no products approved for treatment of sJIA.

In this application, sponsor is seeking approval of TCZ for sJIA based on data from Part-I of study WA18221 which is a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study to evaluate the efficacy and safety of TCZ (12 mg/kg in patients with body weight< 30 kg and 8 mg/kg in patients with body weight ≥30 kg) in patients (n=112) with active sJIA. The dosing regimen is selected based on pharmacokinetic analysis of data from sJIA patients (MRA316JP).

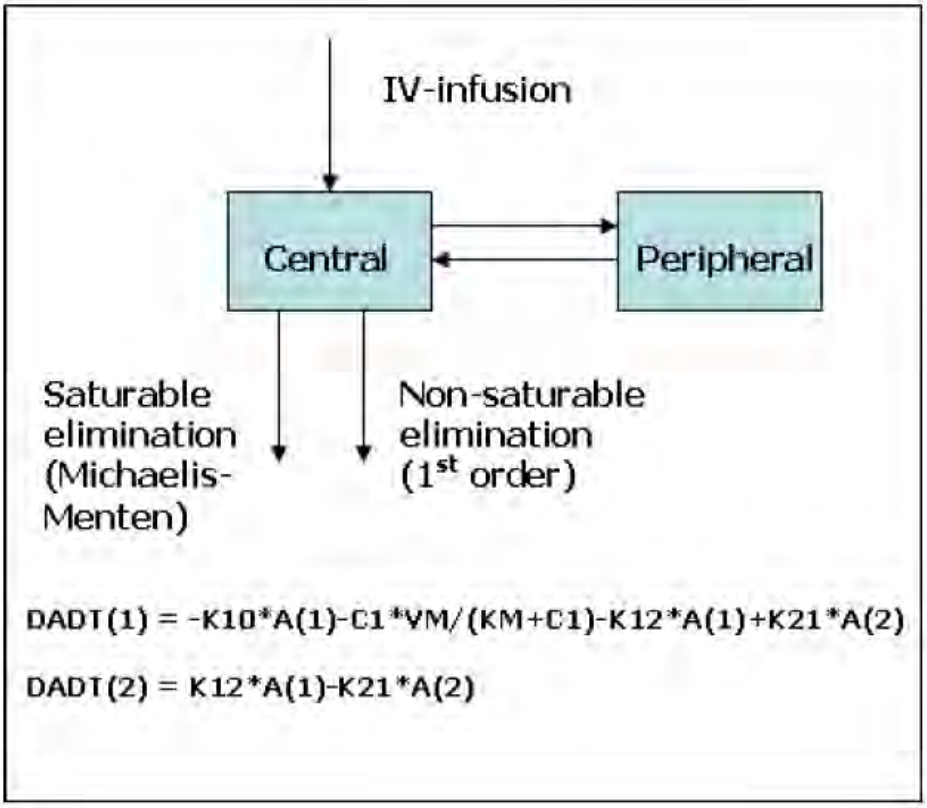
Sponsor collected samples for characterizing TCZ pharmacokinetics in Study WA18221 as shown below:

- one sample at randomization (baseline), before the intake of the first dose of the study medication,
- one pre-dose sample (trough drug levels) on study days 8, 15, 29, 43, 57, 71, 78, and 85,
- One post-dose sample (within 15 minutes of completion of the infusion) on study days 1, 15, 29 and 71.

3 Results of Sponsor's Analysis

Sponsor analyzed TCZ concentration data obtained from Study WA18221 using the pharmacokinetic model as shown in **Figure 4**. The model was developed based on data from LR0320 and MRA316JP studies.

Figure 4. Pediatric structural pharmacokinetic model for TCZ with combined 1st-order and Michaelis-Menten elimination.



Source: Figure 43 on Page 100 of summary-clin-pharm.pdf

Table 9 shows the estimates of pharmacokinetic parameters derived based on the model as shown in **Figure 4**.

Table 9. Summary of population PK parameters from MRA316 & LRO320.

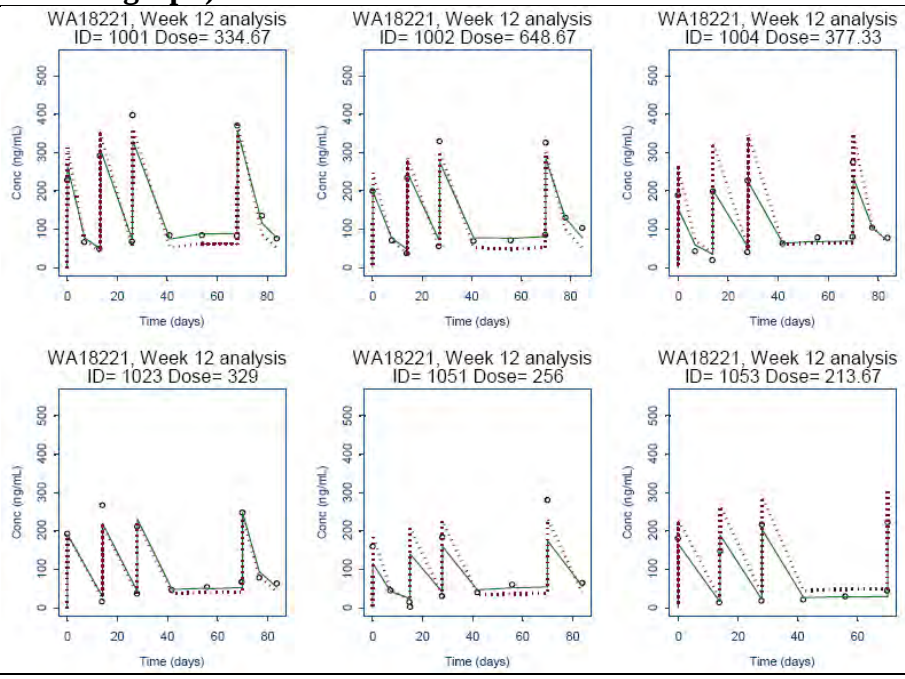
PK parameter	VALUE	SE	CI 5%	CI 95%
CL (L/day)	0.17	0.0079	0.15	0.19
Q (L/day)	4.6	0.43	3.8	5.4
V_c (L)	0.94	0.051	0.84	1
V_p (L)	1.6	0.085	1.4	1.8
Km (mg/L)	2.5	0	0	2.5
V_{max} (mg/day)	3.4	0.49	2.4	4.4
CL_BSA	0.99	0.087	0.82	1.2
Vc_HGT	2	0.23	1.5	2.5
Vc_Age	0.22	0.11	0.0044	0.44
Additive error (mg/L))	3.6	0.46	2.7	4.5
Multiplicative error (%)	15	1.2	13	17

SE-Standard error of estimates; CI-Confidence interval.

Source: Table 41 on Page 101 of summary-clin-pharm.pdf

Using POSTHOC option in NONMEM, sponsor fitted the time course of TCZ concentrations from study WA18221. **Figure 5** shows the observed, population and individual predicted tocilizumab concentration data in representative patients.

Figure 5. Superimposition of observed tocilizumab serum concentrations (open circles), population prediction (dotted line), and individual predicted tocilizumab serum concentrations (solid line) by subject (patient ID and the average dose are indicated on each graph)



Source: Figure 12 on Page 161 of summary-clin-pharm.pdf

Reviewer's Comments: The population pharmacokinetic analysis conducted by the sponsor is acceptable. Figure 2 shows that the mean tocilizumab concentrations are similar between patients (<30kg) treated with 12 mg/kg and patients (≥30 kg) treated with 8 mg/kg. Similar findings are reported based on the population pharmacokinetic analysis as shown in **Table 4**.

4 Reviewer's Analysis

The reviewer was able to reproduce the sponsor's results with NONMEM. No additional analysis was conducted. The following datasets were used in making Figure 3.

Table 10. Analysis Data Sets

Study Number	Name	Link to EDR
wa18221	DEMPK.XPT	\\cber-fs3\m\eCTD_Submissions\STN125276\0025\m5\datasets\wa18221\analysis
wa18221	Nonmem.xpt	\\cber-fs3\M\eCTD_Submissions\STN125276\0025\m5\datasets\wa18221-pk\analysis

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Run1 mod	NONMEM control stream	Z:\Reviews\Ongoing PM Reviews\Tocilizumab_BLA125276_VAB\PPK Analyses\Model\Run1\
Run1.out	NONMEM output file	Z:\Reviews\Ongoing PM Reviews\Tocilizumab_BLA125276_VAB\PPK Analyses\Model\Run1

Signatures

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