

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**125472Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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BLA	125472
Submission Date:	12/21/2012
Brand Name	ACTEMRA®
Submission Type	Original BLA submission
Generic Name	Tocilizumab
OCP Reviewer	Liang Zhao, Ph.D.
Team Leader	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Liang Zhao, Ph.D.
Secondary PM Reviewer	Satjit Brar, Pharm.D., Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Pulmonary, Allergy and Rheumatology Products (DPARP)
Sponsor	Hoffman-La Roche Inc.
Formulation; Strength(s); Administration Route	A single use PFS providing 162 mg of ACTEMRA in 0.9mL; Subcutaneous injection 400 mg per 20 mL
Approved Indications	Treatment of adult patients with moderate to severe active rheumatoid arthritis who have had inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies and treatment of pediatric patients with active systemic juvenile idiopathic arthritis in patients 2 years and older
Proposed Indication	Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs
Approved Dosage Regimen	<p><b>Rheumatoid arthritis (RA)</b></p> <p>Recommended adult dosage every 4 weeks: Patients who have had an inadequate response to one or more TNF antagonists. When used in combination with DMARDs or as monotherapy, the recommended starting dose is 4 mg per kg followed by an increase to 8 mg per kg based on clinical response</p> <p><b>Systemic juvenile idiopathic arthritis (sJIA)</b></p> <p>Recommended sJIA dosage every 2 weeks: 12 mg per kg for patients less than 30 kg weight 8 mg per kg for patients at or above 30 kg weight</p> <p><b>Polyarticular Juvenile Idiopathic Arthritis (pJIA)</b></p> <p>Recommended pJIA dosage every 4 weeks: 10 mg per kg for patients less than 30 kg weight 8 mg per kg for patients at or above 30 kg weight</p>

Proposed Dosage Regimen	Patients less than 100 kg weight	162 mg administered subcutaneously every other week (Q2W), followed by an increase to every week (QW) based on clinical response	
	Patients at or above 100 kg weight	162 mg administered subcutaneously QW	

## Table of Contents

1	Executive Summary .....	4
1.1	Recommendation .....	4
1.2	Phase IV Commitments.....	4
1.3	Summary of Clinical Pharmacology Findings .....	4
2	Question-Based Review (QBR).....	7
2.1	General Attributes .....	7
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?.....	7
2.1.2.	What is the approved therapeutic indication, dosage and route of administration? .....	7
2.2	General Clinical Pharmacology .....	8
2.2.1.	What are the clinical pharmacology and clinical trials used to support the proposed claims? .....	8
2.2.2.	Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?.....	10
2.2.3.	What are the PK characteristics of TCZ in RA patients following SC administration? .....	11
2.2.4.	What are the PD characteristics of tocilizumab in patients?.....	12
2.2.5.	What are the key results from the population PK analysis? .....	12
2.2.6.	Is the proposed dosing regimen justified? .....	12
2.3	Intrinsic Factors .....	14
2.3.1.	What was the impact of demographic covariates on TCZ exposure?.....	14
2.3.2.	What were the immunogenicity findings for TCZ? What was the impact of immunogenicity on exposure, efficacy, and/or safety? .....	14
3	Labeling Recommendation .....	14
4	Appendix: Pharmacometrics Review	

# **1 Executive Summary**

## **1.1 Recommendation**

From a Clinical Pharmacology perspective, the application is acceptable.

## **1.2 Phase IV Commitments**

None.

## **1.3 Summary of Clinical Pharmacology Findings**

### **Pharmacokinetics**

As stated in the label, steady-state mean concentration (Cmean) exposure was similar between 162 mg QW SC and 8 mg/kg IV Q4W regimens (Cmean of 48.6 and 58.4 mcg/mL, respectively). In comparison, trough concentrations were 2.4 times higher (44.6 versus 18.7 mcg/mL) and peak concentrations were 3 times lower (50.9 versus 154.7 mcg/mL) following 162 mg QW SC administration than following 8 mg/kg IV administration. The accumulation ratios for AUC, Cmin, and Cmax were 6.83, 6.37, and 5.47, respectively. Steady state was reached after 12 weeks for AUC, Cmin, and Cmax. All exposure values following 162 mg Q2W SC regimen (9.7, 12.3, and 5.6 mcg/mL for Cmean, peak concentration Cmax, and Ctrough, respectively) were less than half of those following 162 mg QW SC regimen. The accumulation ratios for AUC, Cmin, and Cmax were 2.67, 5.6, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and Cmin, and after 10 weeks for Cmax. Therefore, steady-state TCZ PK exposure were more than dose-proportionally higher following SC QW regimen than following Q2W regimen, which can be explained by significant nonlinear elimination pathway at low TCZ concentrations.

A population PK analysis using data from the first 24-week dosing periods of two Phase III studies (WA22762 and NA25220) was analyzed to assess A two-compartment population PK model with parallel linear and Michaelis-Menten elimination and first order absorption following SC administration were used to describe TCZ concentrations. Based on the population PK analysis, the bioavailability of TCZ following SC administration for a typical patient was estimated to be 79.5% (95%CI: 77.9 – 81.1%). Following SC dosing in rheumatoid arthritis patients, the absorption half-life was around 3-5 days. The t<sub>1/2</sub> of tocilizumab is concentration-dependent. For IV administration, the concentration-dependent apparent t<sub>1/2</sub> is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. For SC administration, the concentration-dependent apparent t<sub>1/2</sub> is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

The developed model had the same structure (with addition of the parameters for bioavailability and absorption) and similar PK parameter values as the population PK model developed earlier based on only IV data, which indicates that there are no differences in PK between IV and SC formulations.

Among all covariate relationships for PK exposure (i.e., HDL-cholesterol on CL, total protein and albumin on volumes, normalized creatinine clearance on VM, age and study on  $k_a$ , and injection site on bioavailability), body weight was identified as the single covariate that significantly influence TCZ CL and volume parameters. Corresponding to a body weight range of 40 and 140 kg, CL decreased and increased respectively by 25% and 47%, and volumes decreased and increased respectively by 32% and 61% relative to the value corresponding to a patient weighting 70 kg.

### Dose justification

Dose justification by the sponsor was relied partially on the developed PK exposure-DAS28 response model, but caveats should be given to interpret the results. The developed model led to the conclusion that the main driver for DAS28 response is TCZ exposure and no other variables have been identified as significant to impact efficacy response. However, two key demographic pieces of information, body weight and geographical region, were not evaluated during covariate model building for DAS28 response. It was observed that patients in the heaviest weight group ( $\geq 100$  kg) and/or patients from in North America had the lowest efficacy responses for both the 162 mg SC QW and the 8 mg/kg IV Q4W regimens. It is also known that drug exposure is positively related to body weight following the 8 mg/kg IV Q4W regimen so less drug exposure in  $\geq 100$  kg body weight group cannot be used as the sole reason for the decreased efficacy. Further assessment of body weight and geographic region effect on DAS28 response is needed for a future generation of the model.

Based on Phase III study results, TCZ 162 mg SC QW and 8 mg/kg IV Q4W treatment regimens demonstrated comparable efficacy. The TCZ 162 SC Q2W dosing regimen also showed clinically superior efficacy improvements to placebo. However, the efficacy effect was less pronounced in the  $> 100$  kg weight group for 162 kg SC Q2W treatment compared to same body weight groups for 162 kg SC QW and 8 mg/kg IV Q4W treatments (50.0%, 50.8%, 38.5%, and 27.3% for 162 mg SC QW, 162 mg SC Q2W, 8 mg/kg IV Q4W, and placebo for ACR20 responses, respectively, at Week 24 in ITT population). By directly comparing the ACR20 responses of patients weighting  $> 100$  kg between SC QW and SC Q2W treatments (i.e., 50.0 % vs. 38.5%), the decreased ACR responses for 162 mg SC Q2W treatment is likely to be associated with less drug exposure. In addition, it was reported that a substantial % of escape patients who escalated from the Q2W SC regimen to the QW SC regimen showed an improvement in efficacy. Therefore, dose escalation from SCQ2W to SC QW for patients weighting  $> 100$  kg to gain therapeutic advantage is reasonable.

Clinical data supported the starting dosing regimen of 162 mg SC Q2W for patients weighting  $< 100$  kg, mainly based on four reasons. First, the efficacy response in terms of ACR20 were observed to be  $>60\%$  for both SC QW and SC Q2W regimens for patients weighting  $< 100$  kg. Second, a higher safety risk was observed across studies for SC QW than for SC Q2W in terms of % of patients with any AE and grades 1 & 2 neutropenia. The exposure–safety model also predicted higher grades 3 & 4 neutropenia risk for QW regimen. Third, overview of AEs leading to dose modifications/ interruptions in studies WA22762 and NA25220 until Week 24 or clinical cutoff in safety population showed that the incidence of such events was higher in the SC QW treatment than in the SC Q2W treatment (27.3% vs. 13.5% at Week 24 and 36.1% vs. 16.7% at

clinical cutoff). Starting from SC Q2W regimen may lend patients the opportunity for safety tolerance development to TCZ regimen and has the advantage of less dose modifications/interruptions. Fourth, the approved IV dosing regimen also recommends starting from a low dose of 4 mg/kg Q4W that can be escalated to 8 mg/kg Q4W based on clinical response.

In summary, the proposed dosing regimen for TCZ SC treatment seems reasonable.

## 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, 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 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<sub>6428</sub>H<sub>9976</sub>N<sub>1720</sub>O<sub>2018</sub>S<sub>42</sub> (polypeptide moiety only).

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

**Dosage form and strength:** A single use PFS providing 162 mg of ACTEMRA in 0.9mL.

#### 2.1.2. What is the approved therapeutic indication, dosage and route of administration?

##### **Indication:**

Rheumatoid Arthritis (RA)

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Systemic Juvenile Idiopathic Arthritis (sJIA)

- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

##### **Dosage and Route of Administration:**

Rheumatoid Arthritis

Recommended Adult Dosage Every 4 Weeks	
Patients who have had an inadequate response to one or more TNF antagonists	When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg followed by an increase to 8 mg per kg based on clinical response.

Systemic Juvenile Idiopathic Arthritis

<b>Recommended SJIA Dosage Every 2 Weeks</b>	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

<b>Recommended IV PJIA Dosage Every 4 Weeks</b>	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

## **2.2 General Clinical Pharmacology**

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

This submission is primarily based on two pivotal phase III clinical trials in patients with RA (NA25220 and WA22762). As included in the submission, there are also a total of six clinical pharmacology studies that were designed to characterize the PK and PD profiles of TCZ following IV and SC administration and to evaluate the immunogenicity of TCZ when administered subcutaneously. Details of the clinical pharmacology studies are listed in Table 1 and the phase III studies including another study being conducted in Japan are listed in Table 2. Study schemes of WA22762 and NA25220 are exhibited in Figures 1 & 2, respectively. PK data for population PK analysis were derived from these two phase III trials (i.e., WA22762 and NA25220).

**Table 1. Overview of Phase I/II Clinical Data on TCZ SC program.**

Study ID	Design	Dose and Regimen	Study Objectives	No of Subjects Enrolled	Status
<b>Clinical Pharmacology Studies</b>					
WP18097	Phase I, single center, single-blind, randomized, placebo-controlled, parallel-group study in healthy subjects.	TCZ 160 mg SC + placebo IV vs TCZ 160 mg IV + placebo SC	Absolute bioavailability of TCZ after SC administration, PK, tolerability	20	Completed
BP22065	Phase I, single-dose, open-label, single center, parallel four-group study in healthy subjects	TCZ 81 mg SC vs TCZ 162 mg SC vs TCZ 162 mg IV vs TCZ 81 mg IV	PK (bioavailability, dose proportionality), safety and tolerability, PK/PD relationship	48	Completed
NP25539	Phase I, single-dose, open-label, parallel, two-group, two-center study in healthy subjects	TCZ 162 mg SC via PFS vs TCZ 162 mg SC via AI	Relative bioavailability of TCZ when given SC via a PFS vs AI; safety and tolerability	261	Completed
MRA227JP	Phase I/II, multi-center, open-label, multiple-dose interindividual, for 35 weeks vs dose escalation study in Japanese patients with RA	Monotherapy with TCZ 81 mg SC q2w vs TCZ 162 mg SC q2w for 35 weeks vs TCZ 162 mg SC qw for 28 weeks	Safety, PK, PD, efficacy, pain on SC administration	32	Completed
NP22623	Phase Ib, multi-center, open-label, randomized, parallel group study in patients with RA.	Part 1: MTX 7.5-25 mg (PO or IV) plus TCZ 162 mg SC qw or q2w for 12 weeks Part 2 (optional post-study phase): TCZ 8 mg/kg IV q4w for up to 1 year	PK, PD, safety, tolerability, injection site reactions and immunogenicity	29	Completed
BP21894	Phase I, partially-randomized, single-dose, open-label, single-center, parallel group study in healthy subjects	TCZ 162 mg SC vs TCZ 162 mg SC + rHuPH2 1350 U vs TCZ 648 mg SC + rHuPH2 5400 U vs TCZ 324 mg SC + rHuPH2 2700 U	Effect of rHuPH2 on exposure to TCZ; PK/PD relationship, safety and tolerability	48	Completed

**Table 2. Overview of Phase III Clinical Data on TCZ SC program.**

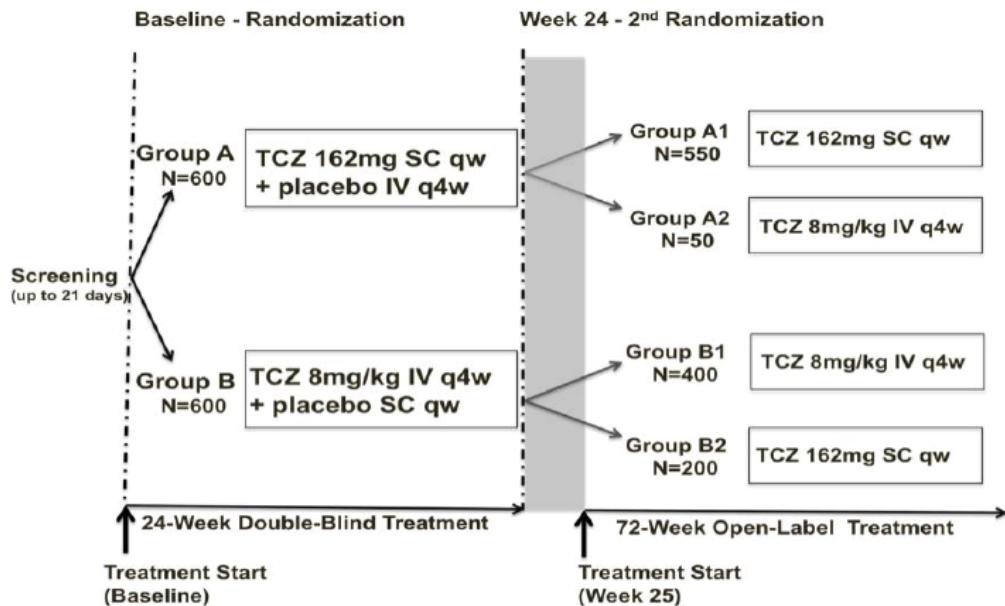
Study ID	Design	Dose and Regimen	Study Objectives	No of Patients Enrolled	Status
<b>Clinical Efficacy Studies</b>					
WA22762 (SUMMACTA)	Phase III, randomized, two-arm, double-blind <sup>a</sup> , double-dummy, active-controlled, parallel-group, multi-center study in patients with RA	DMARD plus either TCZ 162 mg SC qw + placebo IV q4w or TCZ 8 mg/kg IV q4w + placebo SC qw for 24 weeks. At Week 24, re-randomized to open-label TCZ IV or SC for 2 years	Efficacy <sup>b</sup> & safety, PK, PD, immunogenicity; IV to SC switch	1262	Ongoing
NA25220 (BREVACTA)	Phase III, randomized, two-arm, double-blind <sup>a</sup> , placebo-controlled, parallel-group study in patients with RA.	DMARD plus either TCZ 162 mg SC q2w or placebo SC q2w for 24 weeks. At week 24, re-randomized to open-label TCZ 162 mg SC using PFS or AI for up to 2 years	Efficacy <sup>b</sup> & safety, PK, PD, immunogenicity	656	Ongoing
MRA229JP	Phase III, randomized, double-blind <sup>a</sup> , parallel-group comparative study in Japanese patients with RA	Monotherapy with TCZ 162 mg SC q2w + placebo IV q4w vs TCZ 8 mg/kg IV q4w + placebo SC q2w for 24 weeks followed by open-label TCZ 162 mg q2w for 84 weeks	Efficacy <sup>b</sup> , safety, PK	348	Ongoing

AI=auto-injector; DMARD=disease modifying anti-rheumatic drug; IV=intravenous; MTX=methotrexate; PD=pharmacodynamics; PFS=prefilled syringe; PK=pharmacokinetics; PO=oral; qw=once weekly; q2w=every 2 weeks; q4w=every 4 weeks; RA=rheumatoid arthritis; rHuPH2=recombinant human hyaluronidase; SC=subcutaneous; TCZ=tocilizumab; U=units.

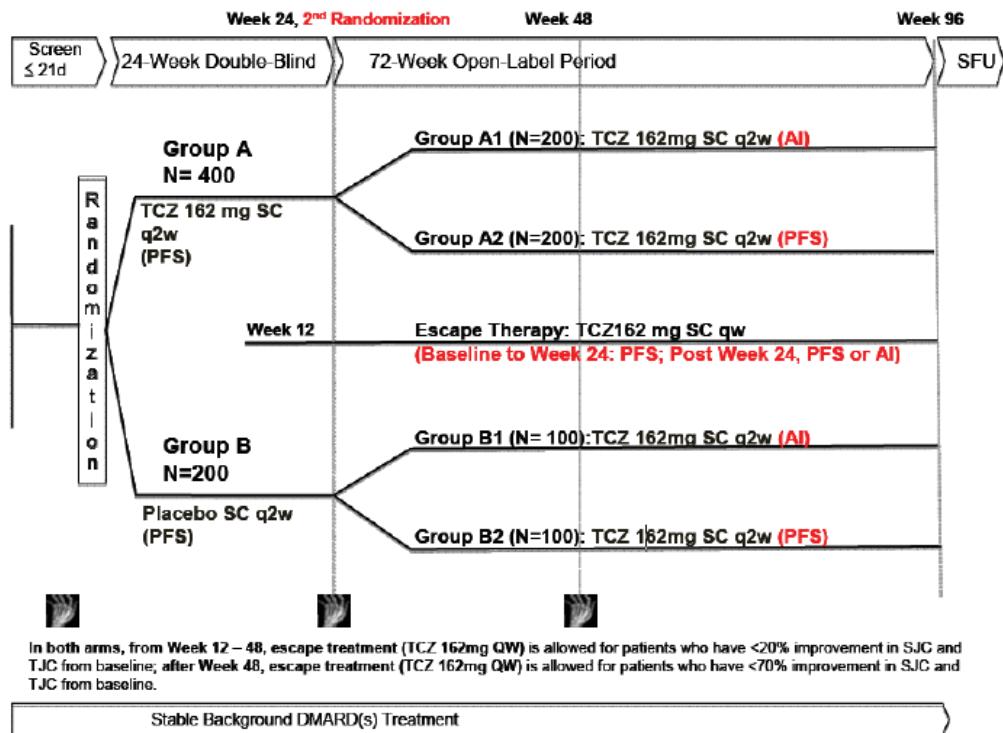
<sup>a</sup> double-blind period was for 24 weeks, followed by an open-label extension period.

<sup>b</sup> primary analysis conducted after patients had completed 24 weeks of treatment.

**Figure 1. Study scheme of WA22762**



**Figure 2. Study scheme of NA25220**



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

Concentrations of TCZ in human serum samples were determined by two different validated sandwich enzyme-linked immunosorbent assays (ELISAs), the Chugai PK assay and Roche PK assay methods. Biotin-labeled interleukin soluble receptor (IL-6 sR) was bound to streptavidin coated microtiter plates in the first step. TCZ in the sample was bound to the immobilized biotin-labeled IL-6 sR. 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 Chugai PK assay stayed the same as used in the original Biologics License Application and Marketing Authorization Application (BLA125276) and was used in Study WP18097. The main assay for this submission (BLA125472) was the Roche assay. This assay was first established and validated at SRL and was used for Chugai studies MRA227JP and MRA229JP. It was also established and validated at [REDACTED] (b)(4). The assay at [REDACTED] (b)(4) was used in Roche studies BP21894, BP22065, NP22623, NP25539, WA22762 (Week 24 and LTE) and NA25220 (Week 24 and LTE). The summary of the assay performance during assay validation at [REDACTED] (b)(4) is shown in Table 3.

Table 3. Performance summary of the TCZ Roche PK Assay in serum from RA patients

Validation Site	Assay Range, ng/mL	Accuracy, %		Precision, %	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
(b)(4)	100 to 3200	94.8 to 115.9	95.3 to 109.2	1.6 to 10.7	5.3 to 9.2

The bioanalytical assays fulfilled the regulatory criterion (refer to the FDA guidance for industry “Bioanalytical Method Validation (Final-May 2001) of not exceeding 15% (20% for the lowest quality control (QC) samples) for precision and accuracy. The accuracy and inter-day precision were acceptable (<15% bias or %CV). Study samples were analyzed in runs containing calibrators and QC samples, as recommended in the FDA guidance. The assay sensitivity in terms of LLOQ (lower limit of quantitation) was 100 ng/mL for TCZ (concentration in native serum).

### 2.2.3. What are the PK characteristics of TCZ in RA patients following SC administration?

TCZ bioavailability was estimated in healthy volunteers by dedicated studies (WP18097 and BP22065) and population PK analysis. By direct comparison of AUC's following a single SC and IV dose of 160 mg, an estimate of absolute bioavailability of 56.5% was observed with study WP18097. As found in study BP22065, at a dose of 162 mg, the bioavailability after SC administration was 48.8%. At 81 mg of TCZ, the absolute bioavailability after SC administration was 22.7%. The increased bioavailability with increased dose reflected more than proportional increase in drug exposure at high SC doses. Therefore, given the nonlinear nature for TCZ clearance, all of these estimates must be taken with caution.

Based on population PK predictions, steady-state Cmean exposure was similar between 162 mg QW SC and 8 mg/kg IV Q4W regimens (Cmean of 48.6 and 58.4 mcg/mL, respectively). In comparison, trough concentrations were 2.4 times higher (44.6 versus 18.7 mcg/mL) and peak concentrations were 3 times lower (50.9 versus 154.7 mcg/mL) following 162 mg QW SC

administration than following 8 mg/kg IV administration. All exposure values following 162 mg Q2W SC regimen (9.7, 12.3, and 5.6 mcg/mL for Cmean, peak concentration Cmax, and Ctrough, respectively) were less than half of those following 162 mg QW SC regimen. Therefore, steady-state TCZ PK exposure were more than dose-proportionally higher following QW SC regimen than following Q2WQ2W regimen, which can be explained by significant nonlinear elimination pathway at low tocilizumab concentrations.

A population PK analysis was conducted to study TCZ bioavailability and PK parameters. A total of 13,642 serum concentrations from 1759 patients from the first 24-week dosing periods of two Phase III studies (WA22762 and NA25220) were analyzed. A two-compartment population PK model with parallel linear and Michaelis-Menten elimination and first order absorption following SC administration were used to describe TCZ concentrations. Based on the population PK analysis, the bioavailability of TCZ following SC administration for a typical patient was estimated to be 79.5% (95%CI: 77.9 – 81.1%). The other estimates for key PK parameters include a linear portion of clearance (CL) of 0.216 L/day (95%CI: 0.211 - 0.221 L/day), a central volume of distribution (V2) of 4.51 L (95%CI: 4.37 - 4.65 L), an inter-compartmental clearance (Q) of 0.274 L/day (95%CI: 0.262 - 0.285 L/day), a peripheral volume of distribution (V3) of 2.77 L (95%CI: 2.68 - 2.87 L), a maximum elimination rate (VM) of 1.85 mg/L/day (95%CI: 1.82 - 1.89 mg/L/day), a Michaelis-Menten constant (KM) of 0.343 µg/mL (95%CI: 0.327 - 0.36 µg/mL), and an absorption rate constant (ka) of 0.233 day-1 (95%CI: 0.221 - 0.246 day-1). The developed model had the same structure (with addition of the parameters for bioavailability and absorption) and similar PK parameter values as the population PK model developed earlier based on only IV data, which indicates that there are no differences in PK between IV and SC formulations.

Among all covariate relationships for PK exposure (i.e., HDL-cholesterol on CL, total protein and albumin on volumes, normalized creatinine clearance on VM, age and study on ka, and injection site on bioavailability), body weight was identified as the single covariate that significantly influence TCZ CL and volume parameters. Corresponding to a body weight range of 40 and 140 kg, CL decreased and increased respectively by 25% and 47%, and volumes decreased and increased respectively by 32% and 61% relative to the value corresponding to a patient weighting 70 kg.

#### **2.2.4. What are the PD characteristics of tocilizumab in patients?**

Based on graphical analysis, it was observed that inflammation biomarkers CRP and ESR decreased with time and with increasing exposure; mechanism based biomarker sIL-6R levels increased with time and with increasing exposure. Post drug treatment, the between subject variability observed in CRP, ESR, and sIL-6R decrease with increasing exposure. Less pronounced effects were seen in CRP, ESR, and sIL-6R responses with the 162 mg SC Q2W regimen than the 162 mg SC QW regimen and 8 mg/kg IV Q4WQ4W regimens.

#### **2.2.5. What are the key results from the population PK analysis?**

See section 2.3.1.

#### **2.2.6. Is the proposed dosing regimen justified?**

The SC dose regimens for the two Phase III studies (WA22762 and NA25220) were determined based on the PK, PD, and safety data from two Phase I/II studies (i.e., MRA227JP and NP22623) in patients with RA. Based on these two study results, it was found that the PD profiles (CRP, ESR, and sIL-6R) corresponding to the TCZ162 mg SC QW regimen were most comparable to those following the 8 mg/kg TCZ IV Q4W regimen. In comparison, the 162 mg SC Q2W regimen led to slower and less pronounced PD responses than 8 mg/kg IV Q4W and 162 mg SC QW regimens. However, the PD responses following the 162 mg SC Q2W regimen were superior to the 81 mg SC Q2W and QW regimens.

Although dose justification by sponsor was partially relied on the developed PK exposure-DAS28 response model, caveats should be given to interpret the results. The developed PK exposure-DAS28 response model led to the conclusion that the main driver for DAS28 response is TCZ exposure and no other variables have been identified as significant to impact efficacy response. However, two key demographic information, body weight and region, were not evaluated during covariate model building for DAS28 response. It was observed that patients in the heaviest weight group ( $>=100$  kg) and/or patients from in North America had the lowest efficacy responses for both the 162 mg SC QW and the 8 mg/kg IV Q4W regimens. It is also known that drug exposure is positively related to body weight following the 8 mg/kg IV Q4W regimen so less drug exposure in  $>=100$  kg body weight group cannot be used as the sole reason for the decreased efficacy. Further assessment of body weight and geographic region effect on DAS28 response is needed for a future generation of the model.

Based on Phase III study results, TCZ 162 mg SC QW and 8 mg/kg IV Q4W treatment regimens demonstrated comparable efficacy. The TCZ 162 SC Q2W dosing regimen also showed clinically superior efficacy improvements to placebo. However, the efficacy effect was less pronounced in the  $> 100$  kg weight group for 162 kg SC Q2W treatment compared to same body weight groups for 162 kg SC QW and 8 mg/kg IV Q4W treatments (50.0%, 50.8%, 38.5%, and 27.3% for 162 mg SC QW, 162 mg SC Q2W, 8 mg/kg IV Q4W, and placebo in terms of ACR20 responses, respectively, at Week 24 in ITT population). By directly comparing the ACR20 responses of patients weighting  $> 100$  kg between SC QW and SC Q2W treatments (i.e., 50.0 % vs. 38.5%), the decreased ACR responses for 162 mg SC Q2W treatment is likely to be associated with less drug exposure. In addition, it was reported that a substantial % of escape patients who escalated from the Q2W SC regimen to the QW SC regimen showed an improvement in efficacy. Therefore, dose escalation from SCQ2W to SC QW for patients weighting  $> 100$  kg to gain therapeutic advantage is reasonable.

Clinical data supported the starting dosing regimen of 162 mg SC Q2W for patients weighting  $< 100$  kg, mainly based on four reasons. First, the efficacy response in terms of ACR20 were observed to be  $>60\%$  for both SC QW and SC Q2W regimens for patients weighting  $< 100$  kg. Second, higher safety risk were observed across studies for SC QW than for SC Q2W in terms of % of patients with any AE and grades 1 & 2 neutropenia. The exposure –safety model also predicted higher grades 3 & 4 neutropenia risk for QW regimen. Third, overview of AEs leading to dose modifications/ interruptions in studies WA22762 and NA25220 until Week 24 or clinical cutoff in safety population showed that the incidence of such events was higher in the SC QW treatment than in the SC Q2W treatment (27.3% vs. 13.5% at Week 24 and 36.1% vs. 16.7% at clinical cutoff). Starting from SC Q2W regimen may lend the opportunity to patients for tolerance development to TCZ regimen and has the advantage of less dose

modifications/interruptions. Fourth, the approved IV dosing regimen also recommends starting from a low dose of 4 mg/kg Q4W that can be escalated to 8 mg/kg Q4W based on clinical response.

In summary, the proposed dosing regimen for TCZ SC treatment seems reasonable. Refer to the appended pharmacometric report for additional dose justification details and the review by Dr. Miya Paterniti, Medical Officer, DPARP, for further information regarding effectiveness/safety of the tested doses.

## **2.3 Intrinsic Factors**

### **2.3.1. What was the impact of demographic covariates on TCZ exposure?**

Body weight was identified as the single covariate that significantly influenced TCZ CL and volume parameters. Corresponding to a body weight range of 40 and 140 kg, CL decreased and increased respectively by 25% and 47%, and volumes decreased and increased respectively by 32% and 61% relative to the value corresponding to a patient weighting 70 kg. The other covariate-exposure relationships identified, which only had insignificant effect on PK profile, include HDL-cholesterol on CL, total protein and albumin on volumes, normalized creatinine clearance on VM, age and study on ka, and injection site on bioavailability. The findings are consistent with population PK models developed for IV formulation, where another body size measure, body surface area (BSA), had been identified as the most influential covariate for TCZ exposure.

Refer to the appended pharmacometric report for additional dose justification details.

### **2.3.2. What were the immunogenicity findings for TCZ? What was the impact of immunogenicity on exposure, efficacy, and/or safety?**

Consistent with immunogenicity (IM) rate reported for TCZ IV, the overall immunogenicity rate for TCZ SC was low (~1%). As inferred from population PK analysis based on two Phase III study data (WA22762 and NA25220), the linear portion of clearance has no appreciable difference between anti-TCZ antibody positive and negative patients. In the population exposure –response analyses of the relationships between exposure and DAS28 and between exposure and neutrophil count, neutralizing anti-TCZ antibodies were not identified as an covariate influencing both TCZ efficacy and safety.

## **3 Labeling Recommendation**

Below is the text added to the approved label for Clinical Pharmacology relevant information. Labeling statements to be removed are shown in ~~strikethrough font~~ and suggested labeling to be included is shown in underline font.

### **Rheumatoid Arthritis—Subcutaneous Administration**

The pharmacokinetics of tocilizumab [REDACTED] <sup>(b) (4)</sup> using a population pharmacokinetic analysis [REDACTED] <sup>(b) (4)</sup> a database composed of 1759 rheumatoid arthritis patients treated with 162 mg SC every week, 162 mg SC every other week, and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. For the 162 mg every week dose, the [REDACTED] <sup>(b) (4)</sup> estimated mean ( $\pm$ SD) steady-state AUC<sub>1week</sub>, C<sub>min</sub> and C<sub>max</sub> of tocilizumab were  $8200 \pm 3600$  mcg•h/mL,  $44.6 \pm 20.6$  mcg/mL, and  $50.9 \pm 21.8$  mcg/mL, respectively. The accumulation ratios for AUC, C<sub>min</sub>, and C<sub>max</sub> were 6.83, 6.37, and 5.47, respectively. Steady state was reached after 12 weeks for AUC, C<sub>min</sub>, and C<sub>max</sub>.

For the 162 mg every other week dose, the [REDACTED] <sup>(b) (4)</sup> estimated mean ( $\pm$ SD) steady-state AUC<sub>2week</sub>, C<sub>min</sub>, and C<sub>max</sub> of tocilizumab were  $3200 \pm 2700$  mcg•h/mL,  $5.6 \pm 7.0$  mcg/mL, and  $12.3 \pm 8.7$  mcg/mL, respectively. The accumulation ratios for AUC, C<sub>min</sub>, and C<sub>max</sub> were 2.67, 5.6, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C<sub>min</sub>, and after 10 weeks for C<sub>max</sub>.

## Absorption

Following SC dosing in rheumatoid arthritis patients, the absorption half-life was around [REDACTED] <sup>(b) (4)</sup> days. The estimated steady state bioavailability for the SC formulation was around 0.8 at the therapeutic doses.

## Elimination

The t<sub>1/2</sub> of tocilizumab is concentration-dependent. For IV administration, the concentration-dependent apparent t<sub>1/2</sub> is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. For SC administration, the concentration-dependent apparent t<sub>1/2</sub> is up to 13 days for 162 mg every week and up to 5 days for 162 mg every other week in patients with RA at steady-state.

## APPENDIX: PHARMACOMETRICS REVIEW

### 1 SUMMARY OF FINDINGS

#### 1.1 Key Review Questions

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

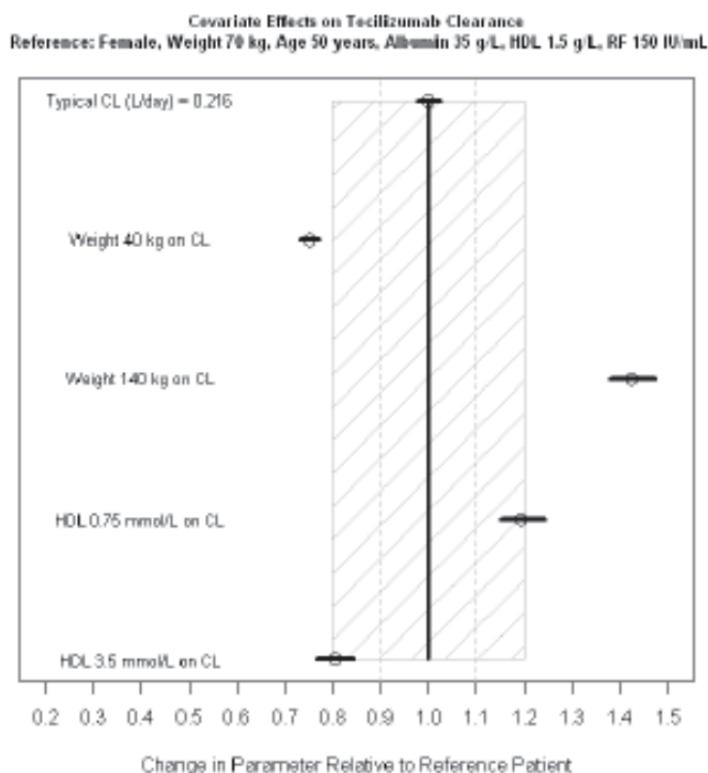
##### 1.1.1 What are the main population PK findings for tocilizumab (TCZ) dose/dosing regimen in rheumatoid arthritis (RA) patients following subcutaneous (SC) administration?

Among all the covariates explored, body weight was identified as the only significant covariate on TCZ clearance and volume of distribution. Based on the final model, patients weighing 40 and 140 kg are associated with decreased and increased clearance (CL) by 25% and 43%, respectively, compared to a patient weighing 70 kg. Moreover, volume of distribution (VD) decreased and increased by 32% and 61% respectively, compared to a patient weighing 70 kg. These covariate findings support the weight-derived dosing regimen.

A developed 2-compartment population PK (popPK) model adequately described the time course of serum TCZ concentration following SC administration in subjects with active RA. In the model, total CL is the sum of both linear (concentration-independent) and nonlinear (concentration-independent) components. For the linear elimination pathway, a mean CL of around 9 mL/h was estimated from the final popPK model. The nonlinear elimination pathway of TCZ is believed to describe a target-mediated clearance process due to the binding to the target IL-6R. It was estimated that a linear PK profile will be observed at TCZ serum concentrations of > 40 µg/mL. The saturation of the nonlinear elimination pathway was more pronounced with the 162 mg QW SC and the 8 mg/kg Q4W IV regimen, resulting in less variation of total clearance over the dosing interval at steady-state compared to 162 mg Q2W SC dosing. Due to the dependence of total clearance on TCZ serum concentrations, the half-life of TCZ is also concentration-dependent. Based on the popPK model, an effective half-life was estimated for TCZ serum concentrations at steady-state. During an inter-dose interval at steady state, the effective steady state half-life of TCZ was found to be between 12.1 and 13.0 days for 162 mg SC QW regimen and between 1.8 and 4.9 days for 162 mg SC Q2W regimen and between 6.6 and 18.6 days for 8 mg/kg IV Q4W regimen, based on the predicted concentration range at terminal phase. Following TCZ SC administration, the absorption half-life was estimated to be between 4 to 5 days and the bioavailability of TCZ was estimated to be 79.5% (95%CI: 77.9 – 81.1%).

The final PK model based on data from Studies NA25220 and WA22762 retained the effects of weight and HDL-cholesterol on CL; weight, total protein and albumin on central and peripheral volumes; normalized creatinine clearance on Vmax; age and study on ka; and injection site on bioavailability. The covariate effect on exposure was assessed by referring to the observed range and the results were demonstrated in **Figure 1**.

**Figure 1 Covariate effects on TCZ clearance.**



Source: Figure 66 from report of Population PK Analysis of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

### 1.1.2 What is the rationale behind the proposed tocilizumab (TCZ) dose/dosing regimen in rheumatoid arthritis (RA) patients following subcutaneous (SC) administration?

The following shows the proposed TCZ dosing regimen in patients with RA:

Patients less than 100 kg weight	<ul style="list-style-type: none"> <li>162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response</li> </ul>
Patients at or above 100 kg weight	<ul style="list-style-type: none"> <li>162 mg administered subcutaneously every week</li> </ul>

The SC dose regimens for the two Phase III studies (studies WA22762 and NA25220) were determined based on the PK, PD, and safety data from two Phase I/II studies (i.e., MRA227JP and NP22623) in patients with RA. Based on these two study results, it was

found that the PD profiles (e.g., CRP, ESR, and sIL-6R) corresponding to the TCZ162 mg SC QW regimen were most comparable to those following the 8 mg/kg TCZ IV Q4W regimen. In comparison, the 162 mg SC Q2W regimen led to slower and less pronounced PD responses than 8 mg/kg IV Q4W and 162 mg SC QW regimens. However, the PD responses following the 162 mg SC Q2W regimen were superior to the 81 mg SC Q2W and QW regimens. Both a population PK model and exposure-response models for both efficacy and safety have been used to justify the SC dosing regimen.

Although dose justification by sponsor was partially relied on the developed PK exposure-DAS28 response model, caveats should be given to interpret the results. The developed PK exposure-DAS28 response model led to the conclusion that the main driver for DAS28 response is TCZ exposure and no other variables have been identified as significant to impact efficacy response. However, two key demographic information, body weight and region, were not evaluated during covariate model building for DAS28 response. It was observed that patients in the heaviest weight group ( $\geq 100$  kg) and/or patients from North America had the lowest efficacy responses for both the 162 mg SC QW and the 8 mg/kg IV Q4W regimens. It is also known that drug exposure is positively related to body weight following the 8 mg/kg IV Q4W regimen so less drug exposure in  $\geq 100$  kg body weight group cannot be used as the sole reason for the decreased efficacy. Further assessment of body weight and geographic region effect on DAS28 response is needed for a future generation of the model.

Based on Phase III study results, TCZ 162 mg SC QW and 8 mg/kg IV Q4W treatment regimens demonstrated comparable efficacy. The TCZ 162 SC Q2W dosing regimen also showed clinically superior efficacy improvements to placebo. However, the efficacy effect was less pronounced in the  $> 100$  kg weight group for 162 kg SC Q2W treatment compared to same body weight groups for 162 kg SC QW and 8 mg/kg IV Q4W treatments (50.0%, 50.8%, 38.5%, and 27.3% for 162 mg SC QW, 162 mg SC Q2W, 8 mg/kg IV Q4W, and placebo in terms of ACR20 responses, respectively, at Week 24 in ITT population). By directly comparing the ACR20 responses of patients weighting  $> 100$  kg between SC QW and SC Q2W treatments (i.e., 50.0 % vs. 38.5%), the decreased ACR responses for 162 mg SC Q2W treatment is likely to be associated with less drug exposure. In addition, it was reported that a substantial % of escape patients who escalated from the Q2W SC regimen to the QW SC regimen showed an improvement in efficacy. Therefore, dose escalation from SCQ2W to SC QW for patients weighting  $> 100$  kg to gain therapeutic advantage is reasonable.

Clinical data supported the starting dosing regimen of 162 mg SC Q2W for patients weighting  $< 100$  kg, mainly based on four reasons. First, the efficacy response in terms of ACR20 were observed to be  $> 60\%$  for both SC QW and SC Q2W regimens for patients weighting  $< 100$  kg. Second, higher safety risk were observed across studies for SC QW than for SC Q2W in terms of % of patients with any AE and grades 1 & 2 neutropenia. The exposure –safety model also predicted higher grades 3 & 4 neutropenia risk for QW regimen. Third, overview of AEs leading to dose modifications/ interruptions in studies WA22762 and NA25220 until Week 24 or clinical cutoff in safety population showed that the incidence of such events was higher in the SC QW treatment than in the SC Q2W treatment (27.3% vs. 13.5% at Week 24 and 36.1% vs. 16.7% at clinical cutoff). Starting from SC Q2W regimen may lend patients the opportunity for safety tolerance

development to TCZ regimen and has the advantage of less dose modifications/interruptions. Fourth, the approved IV dosing regimen also recommends starting from a low dose of 4 mg/kg Q4W that can be escalated to 8 mg/kg Q4W based on clinical response.

In summary, the proposed dosing regimen for TCZ SC treatment seems reasonable.

## **1.2 Recommendations**

Please see proposed changes to labeling statements.

## **1.3 Label Statements**

See Clinical Pharmacology review.

# **2 RESULTS OF SPONSOR'S ANALYSIS**

## **2.1 Population PK analysis**

### **2.1.1 Analysis Dataset**

The population PK database included dosing, PK and covariate data from the Phase III studies, WA22762 and NA25220. There were 13,642 samples from 1759 patients used in the analysis with the combined dataset.

### **2.1.2 Model building**

The structural popPK model is an empirical two-compartment PK model with a first-order absorption to describe SC administration and both parallel linear and Michaelis-Menten eliminations. The nonlinear elimination pathway of tocilizumab was believed to represent a target-mediated clearance process due to the binding to IL-6R. Nonlinear mixed-effect modeling was conducted using NONMEM (version 7.2.0).

By engaging prior learnings from the popPK model for TCZ IV, a covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was used for covariate selection. A full model was established by incorporating potential covariate-parameter relationships identified based on prior learning, mechanistic plausibility, and exploratory graphics. The full model did not initially include strongly correlated or collinear covariates. Additional exploratory diagnostics for the full covariate model was conducted by graphical exploration of all measured covariate effects and the model was revised when necessary. The relationships suggested by the diagnostic plots of the base model were also tested.

The effects of continuous covariates were modeled using a normalized power model while the effects of binary covariates were modeled by factor multiplication.

In summary, weight, BSA, sex, age, albumin, rheumatoid factor, and HDL-cholesterol were considered for CL; weight, BSA, sex, age, albumin, and total protein for central and peripheral volumes; age, injection site, weight, and BMI for absorption rate constant; injection site, weight, and BMI for bioavailability; albumin, normalized creatinine clearance, and smoking for VM constant. The base and covariate models developed with the dataset from Study WA22762 were updated, after performing external validation with dataset from Study NA25220, using the pooled dataset from Studies WA22762 and NA25220.

*Reviewer's comment: no formal covariate selection procedure has been implemented for the popPK model for TCZ SC. However, given the model building procedure and validation for the popPK model for TCZ IV and the various model validation techniques used for the popPK model for TCZ SC, the model building procedure implemented for TCZ SC is reasonable.*

### 2.1.3 Model evaluation

The developed models were extensively evaluated by basic graphical evaluations, ETA shrinkage, and predictive checks.

Basic graphical evaluations included graphical plots checking Observed Concentrations (DV) vs predicted concentrations (Population prediction (PRED), individual predictions (IPRED)), residual plots (conditional weighted residuals (CWRES), individual weighted residuals (IWRES) vs predictions and time), histograms and quantile-quantile plots (conditional weighted residuals and individual random effects (IIV)), plots for individual random effects (intercorrelations and relationship to covariates).

For ETA shrinkage, the shrinkage percent for random effect  $\eta_i$  is calculated by the following equation:

$$\text{Shrinkage}_i = 100 \left( 1 - \frac{SD_i}{\sqrt{\Omega(i,i)}} \right)$$

Here SD<sub>i</sub> was the standard deviation of the individual random effects estimates and  $\Omega(i,i)$  was the corresponding diagonal term of the random effects variance-covariance matrix estimated by the model.

The employed predictive check procedures include Visual Predictive Check (VPC), Predictive Check Simulations (PCS) for the trough concentrations at week 24, Standardized Visual Predictive Check (SVPC), and Normalized Prediction Distribution Errors (NPDE).

### 2.1.4 Results

In summary, the developed two-compartment population PK model adequately characterized the time course of serum TCZ concentration following SC administration in subjects with active RA, as supported by all model evaluation approaches employed. In the model, total CL was defined as the sum of both a linear (concentration-independent) component and a nonlinear (concentration-dependent) component.

Based on the final model, a mean linear CL was estimated to be ~ 9 mL/h. The nonlinear elimination pathway of TCZ was believed to reflect the target-mediated clearance process as a result of TCZ binding to IL-6R. Based on the final model, it was expected that linear PK profile be apparent at TCZ serum concentrations of > 40 µg/mL. Therefore, the saturation of the nonlinear elimination pathway was more pronounced for the 162 mg SC QW and 8 mg/kg IV Q4W regimen, resulting in less variation of total clearance and thus drug exposure over the dosing interval at steady-state compared to 162 mg SC Q2W dosing regimen. It was also expected that the half-life of TCZ be also concentration-dependent, given target mediated drug clearance and the dependence of total drug clearance on TCZ serum concentrations. Based on estimates from the final model and

Tocilizumab (BLA125472)

Page 5 of 27

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simulations, the effective steady state half-life of TCZ was found to be between 1.8 and 4.9 days, between 12.1 and 13.0 days, and between 6.6 and 18.6 for 162 mg SC Q2W, 162 mg SC QW regimen, and 8 mg/kg IV Q4W regimen, respectively, based on their concentration range in the terminal phase. Following TCZ SC administration, the absorption halflife was estimated to be between 4 to 5 days. The bioavailability of TCZ following SC administration was estimated to be 79.5% (95%CI: 77.9 – 81.1%).

Based on model simulations, PK parameters following different SC regimens were simulated. For the 162 mg every week dose, the estimated mean ( $\pm$ SD) steady-state AUC<sub>1 week</sub>, Cmin and Cmax of tocilizumab were  $8200 \pm 3600$  mcg•h/mL,  $44.6 \pm 20.6$  mcg/mL, and  $50.9 \pm 21.8$  mcg/mL, respectively. The accumulation ratios for AUC, Cmin, and Cmax were 6.83, 6.37, and 5.47, respectively. Steady state was reached after 12 weeks for AUC, Cmin, and Cmax. For the 162 mg every other week dose, the estimated mean ( $\pm$ SD) steady-state AUC<sub>2 week</sub>, Cmin, and Cmax of TCZ were  $3200 \pm 2700$  mcg•h/mL,  $5.6 \pm 7.0$  mcg/mL, and  $12.3 \pm 8.7$  mcg/mL, respectively. The accumulation ratios for AUC, Cmin, and Cmax were 2.67, 5.6, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and Cmin, and after 10 weeks for Cmax.

The final PK model retained the effects of weight and HDL-cholesterol on CL; weight, total protein and albumin on central and peripheral volumes; normalized creatinine clearance on VM; age and study on ka; and injection site on bioavailability. PK parameters associated with the final model is shown in Table 1. The covariate effect on exposure was assessed by referring to the observed range and the results were demonstrated in Table 2 and Figure 2. Among all identified covariate relationships body weight was identified as the only significant covariate on TCZ clearance and volume of distribution. Based on the final model, patients weighting 40 and 140 kg are associated with decreased and increased CL by 25% and 43%, and are associated with volume of distributions decreased and increased respectively by 32% and 61% respectively, compared to a patient weighting 70 kg. The negative correlation between body weight and drug exposure was verified by exploratory analysis as demonstrated by Figure 3.

Simulations based on the final model were conducted to derive PK exposure parameters based on dosing regimen and body weight (<60 kg, 60-100 kg, and  $\geq 100$  kg). Summary statistics of predicted individual steady-state exposure parameters were shown in Table 3.

Table 1 PopPK parameter estimates from the final popPK model.

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
CL (L/day)	$\theta_1$	0.216	1.18	0.211 - 0.221		
V <sub>2</sub> (L)	$\theta_2$	4.51	1.61	4.37 - 4.65		
Q (L/day)	$\theta_3$	0.274	2.2	0.262 - 0.285		
V <sub>3</sub> (L)	$\theta_4$	2.77	1.7	2.68 - 2.87		
V <sub>M</sub> (mg/L/day)	$\theta_5$	1.85	1.04	1.82 - 1.89		
K <sub>M</sub> (mcg/mL)	$\theta_6$	0.343	2.49	0.327 - 0.36		
k <sub>a</sub> (1/day)	$\theta_7$	0.233	2.68	0.221 - 0.246		
F <sub>SC</sub>	$\theta_8$	0.795	1.05	0.779 - 0.811		
CL <sub>WT</sub> , Q <sub>WT</sub>	$\theta_9$	0.512	4.36	0.468 - 0.555		
V <sub>2WT</sub> , V <sub>3WT</sub>	$\theta_{10}$	0.683	3.86	0.631 - 0.735		
CL <sub>HDL</sub>	$\theta_{11}$	-0.256	10.9	-0.311 - -0.201		
V <sub>ALB</sub>	$\theta_{12}$	-0.672	9.38	-0.796 - -0.548		
V <sub>PROT</sub>	$\theta_{13}$	0.728	12.2	0.554 - 0.901		
V <sub>M,CRCLN</sub>	$\theta_{14}$	0.229	7.43	0.196 - 0.263		
k <sub>a,AGE</sub>	$\theta_{15}$	-0.442	17.2	-0.592 - -0.293		
k <sub>a,NA25220</sub>	$\theta_{16}$	0.61	3.54	0.568 - 0.652		
F <sub>SC,SJIT3</sub>	$\theta_{17}$	1.11	0.712	1.09 - 1.12		
$\sigma_{NA25220}$	$\theta_{18}$	1.94	3.1	1.83 - 2.06		
$\omega^2_{CL}$	$\Omega(1,1)$	0.076	4.49	0.0693 - 0.0827	CV=27.6	17.0%
$\omega^2_{V2}$	$\Omega(2,2)$	0.0507	5.04	0.0457 - 0.0557	CV=22.5	10.8%
R $\omega_{V2}\omega_{V3}$	$\Omega(2,3)$	0.045	8.26	0.0377 - 0.0523	R=0.661	0
$\omega^2_{V3}$	$\Omega(3,3)$	0.0915	7.22	0.0786 - 0.104	CV=30.3	21.6%
$\omega^2_{ka}$	$\Omega(4,4)$	0.216	6.3	0.19 - 0.243	CV=46.5	23.4%
$\omega^2_{EPS}$	$\Omega(5,5)$	0.289	3.72	0.268 - 0.31	CV=53.8	-2.8%
$\sigma^2$	$\Sigma(1,1)$	0.0431	3.99	0.0397 - 0.0464	CV=20.7	3.2%

PE: Parameter Estimate; 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 %.

CL – drug clearance, V2 – central volume of distribution, Q – inter-compartmental clearance, V3 – peripheral volume of distribution, VM – maximum elimination rate, KM – Michaelis-Menten constant, Ka – absorption rate, Fsc – bioavailability, WT – weight, HDL – HDL cholesterol, PROT – total protein, ALBU – albumin, CRCLN – normalized creatinine clearance, CV - coefficient of variation,  $\theta$  – fixed effect parameter,  $\Omega$  – inter-individual covariance matrix,  $\omega$  – inter-individual variance,  $\sigma$  – standard error

Source: Table 17 from report of Population PK Analysis of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

Table 2 Predicted covariate effect by the final model.

Parameters	Covariate				Effect (CI) %
	Name (Units)	Range	Reference	Value	
CL	Weight (kg)	34.4 - 149	70	40	-24.9 [-26.8; -22.9]
				140	42.6 [38; 47.2]
V <sub>2</sub> , V <sub>3</sub>	HDL (mmol/L)	0.31 - 4.46	1.5	0.75	19.4 [15; 24.1]
				3.5	-19.5 [-23.2; -15.7]
V <sub>M</sub>	Weight (kg)	34.4 - 149	70	40	-31.8 [-33.7; -29.8]
				140	60.6 [54.9; 66.4]
V <sub>2</sub> , V <sub>3</sub>	Albumin (g/L)	22 - 49	35	25	25.4 [20.3; 30.7]
	Protein (g/L)	59 - 96		50	-21.3 [-24.7; -17.8]
V <sub>M</sub>	Normalized Creatinine Clearance (mL/min/1.73m <sup>2</sup> )	28.4 - 251 (restricted by 150 in the model)	100	50	-14.7 [-16.6; -12.7]
				150	9.7 [8.3; 11.2]
k <sub>a</sub>	Age (years)	18 - 86	50	30	25.4 [16.1; 35.3]
				80	-18.8 [-24.3; -12.9]
F <sub>sc</sub>	Study	27262/22520	27262	22520	-39 [-43.3; -34.7]
	Injection Site	Arm/Abdomen/Thigh/Unknown	Arm/Abdomen/unknown	Thigh	10.9 [9.3; 12.4]

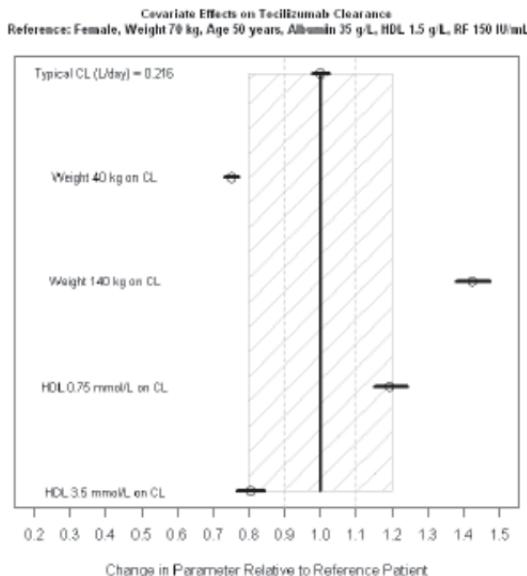
Source: Table 19 from report of Population PK Analysis of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

Table 3 Summary statistics of predicted individual steady-state exposure parameters by dosing regimen and weight (<60 kg, 60-100 kg, and >= 100 kg).

Dose Regimen	N	Weight (kg)		AUC <sub>T</sub> ( $\mu\text{g}/\text{mL}\cdot\text{day}$ )	C <sub>mean</sub> ( $\mu\text{g}/\text{mL}$ )	C <sub>max</sub> ( $\mu\text{g}/\text{mL}$ )	T <sub>max</sub> (day)	C <sub>trough</sub> ( $\mu\text{g}/\text{mL}$ )	
		Cut-off Range	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
SC 162 mg qw	143	< 60	52.1 (5.3)	470.5 (157.2)	67.2 (22.5)	69.7 (22.7)	2.8 (0.3)	62.6 (22.1)	
	420	60 - 100	76.8 (10.8)	323.7 (135.7)	46.2 (19.4)	48.3 (19.7)	2.8 (0.3)	42.4 (19)	
	58	≥ 100	114.1 (12.8)	178.8 (97.3)	25.5 (13.9)	26.9 (14.2)	2.9 (0.3)	23 (13.5)	
SC 162 mg q2w	136	< 60	52.8 (4.8)	220.4 (113.1)	15.7 (8.1)	19 (8.9)	4.9 (0.4)	10.2 (6.9)	
	346	60 - 100	73.9 (10.6)	121.7 (88.1)	8.7 (6.3)	11.2 (6.9)	4.7 (0.5)	4.6 (5.3)	
	27	≥ 100	111.9 (10.2)	48.3 (37.1)	3.5 (2.6)	5.2 (3.3)	4.1 (0.8)	1 (1.6)	
8 mg/kg IV q4w	146	< 60	53 (5.3)	1338.8 (461.7)	47.8 (16.5)	129.8 (31.1)	-	13.2 (11.4)	
	416	60 - 100	75.7 (10.6)	1649.3 (493.8)	58.9 (17.6)	152.9 (34.7)	-	18.8 (12.7)	
	67	≥ 100	114.1 (12.3)	2282.3 (928.1)	81.5 (33.1)	201.8 (59.5)	-	31 (23.5)	
		Median [range]		Median [range]		Median [range]		Median [range]	
SC 162 mg qw	143	< 60	53.1 [38-59.6]	452.6 [129-1038]	64.7 [18.4-148.3]	68 [19.1-150.1]	3 [2-3.5]	59.8 [17.3-145.2]	
	420	60 - 100	75.9 [60-100]	311.5 [16.3-905.4]	44.5 [2.3-129.3]	46.4 [2.9-132.6]	3 [2-3.5]	40.5 [1.3-123.4]	
	58	≥ 100	111 [100-149.1]	154 [25.4-447.8]	22 [3.6-64]	23.2 [4.4-65.6]	3 [2.5-3.5]	19.7 [2.2-61.2]	
SC 162 mg q2w	136	< 60	53.7 [37.1-59.7]	212 [34.1-607.5]	15.1 [2.4-43.4]	17.9 [4-48.7]	5 [4-5.5]	10.6 [0.2-34.4]	
	346	60 - 100	71.5 [60-99.8]	92.6 [8.8-467.5]	6.6 [0.6-33.4]	9.3 [1.1-37.9]	4.5 [3-6.5]	2.6 [0.1-28.3]	
	27	≥ 100	108.5 [100.3-132]	40.8 [3-154.5]	2.9 [0.2-11]	5 [0.4-14.5]	4.5 [1.5-5.5]	0.2 [0-5.8]	
8 mg/kg IV q4w	146	< 60	54 [34.4-59.8]	1260.1 [461.4-3199]	45 [16.5-114.3]	126.3 [64.1-248.6]	-	10.6 [0.1-61.5]	
	416	60 - 100	73.9 [60-99.9]	1585.2 [684.8-3498.6]	56.6 [24.5-124.9]	152.6 [69.2-266.9]	-	16.4 [0.1-68.3]	
	67	≥ 100	111.5 [100-148.6]	2146.7 [766-7296.5]	76.7 [27.4-260.6]	200.6 [99.1-492]	-	24.3 [0.2-158.7]	

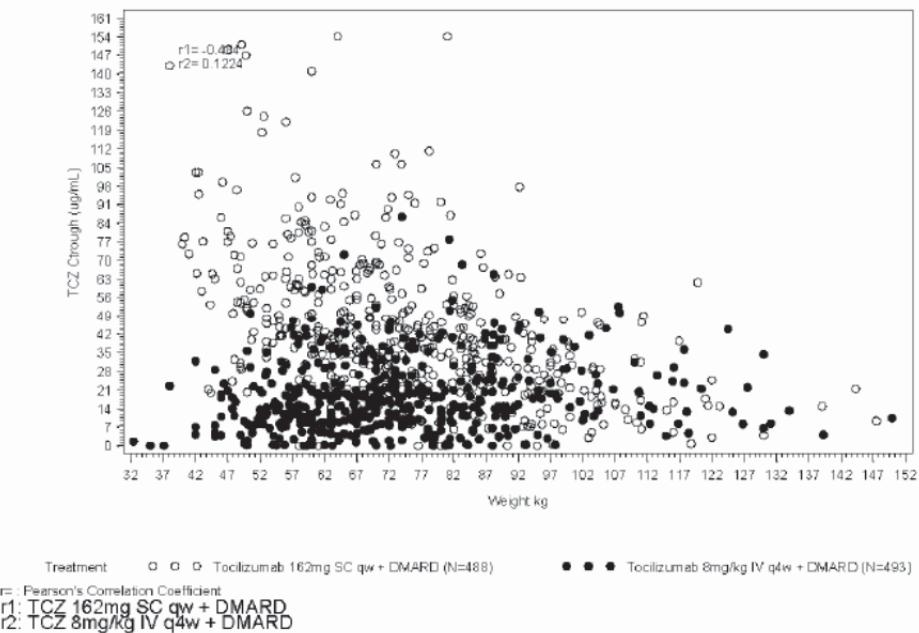
Source: Table 19 from report of Population PK Analysis of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

**Figure 2 Covariate effects on TCZ clearance.**



Source: Figure 66 from report of Population PK Analysis of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

**Figure 3 Observed C<sub>trough</sub> at Week 24 versus body weight at Week 20.**



Source: Figure 13 from report of Population PK Analysis of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis.

## **2.2 Exposure-efficacy response (DAS28) analysis**

### **2.2.1 Analysis Dataset**

The dataset for exposure-response analysis contained DAS28 measurements from a total of 1890 subjects (i.e., 9430 DAS28 measurements from 1250 subjects of study WA22762 and 4568 measurements from 640 subjects of study NA25220). Among the 1890 subjects, 629, 621, 353, and 126 subjects received 8 mg/kg Q4W IV, 162 mg QW SC, 162 mg Q2W SC, or placebo TCZ doses, respectively; 90 and 71 subjects received placebo or 162 mg Q2W SC doses for 12 weeks , respectively, but escaped after week 12 by switching to 162 mg TCZ QW SC dosing regimen. DAS28 data were not available after week 12 for the majority of escaped subjects.

### **2.2.2 Model building**

The time-course of DAS28 was described by an indirect-response model with inhibition of production rate driven by serum TCZ concentrations, which was also used to model the time-course of DAS28 following IV administration. TCZ was assumed to inhibit ‘production’ of DAS28 via an Emax function.

Full model with backward elimination was used to identify the final covariate model. Potential covariate-parameter relationships were identified based on scientific interest, mechanistic plausibility, and exploratory graphics, and were incorporated into the full model simultaneously with the notion not to include strongly correlated or collinear covariates. The full model development was also assisted by the additional graphical exploration of the measured covariate values vs estimates of individual random effects from the full model. During backward elimination, (1) precisely estimated covariates with clinically insignificant effects and (2) covariates with effects close to null value and/or with high relative standard error and/or with the 95% confidence intervals that included the null value were excluded from the final model. Increase of objective function value by less than 10.83 at a single covariate elimination was used as a criterion to exclude covariates, which was equivalent to eliminate covariates associated with wide covariate effect confidence intervals that were not statistically significant at  $\alpha=0.001$  level.

The following covariates were screened for their effects on efficacy: gender, age, baseline C-reactive protein (CRP) and IL6, previous treatment with corticosteroids (PCOR), baseline values of health assessment questionnaire (HAQ), patient’s assessment of pain (PAIN), and physicians global score of disease activity (VASP) on the baseline value of DAS28; gender, age, baseline CRP, and PCOR on the first order elimination rate of DAS28 (kout in model); gender, age, and baseline CRP and IL6 on the TCZ concentration at which 50% of the maximum effect is reached (EC50 in model) and LEmax (LEmax defined with a relation to maximum drug effect Emax with a relation  $\text{Emax}=1/(1+LEmax)$  in model); and baseline IL6 on the background effect of cocomitant DMARD therapies expressed in TCZ concentration equivalents ( $C_{\text{DMARD}}$ ). The rationale for exploring these covariates was based on clinical importance, mechanistic plausibility, and prior knowledge from the previous analysis.

### **2.2.3 Model evaluation**

The developed models were extensively evaluated by basic graphical evaluations, ETA shrinkage, and predictive checks.

Basic graphical evaluations included graphical plots checking Observed DAS28 values (DV) vs predicted concentrations (Population prediction (PRED), individual predictions (IPRED)) and time, residual plots (absolute conditional weighted residuals, individual weighted residuals (IWRES) vs predictions and time), histograms and quantile-quantile plots (conditional weighted residuals and individual random effects (IIV)), plots for individual random effects (intercorrelations and relationship to covariates) and their distribution plots stratified by the categorical covariates.

For ETA shrinkage, the shrinkage percent for each random random effect  $\eta_i$  is calculated by the following equation:

$$Shrinkage_i = 100 \left( 1 - \frac{SD_i}{\sqrt{\Omega(i,i)}} \right)$$

Here SD<sub>i</sub> was the standard deviation of the individual random effects estimates and  $\Omega(i,i)$  was the corresponding diagonal term of the random effects variance-covariance matrix estimated by the model.

The precision of for parameter estiamtes were provided for each of the parameters and non-parametric bootstrap procedure is employed due to long run time for each iteration. The employed predictive check procedures include Visual Predictive Check (VPC), Predictive Check Simulations (PCS), Standardized Visual Predictive Check (SVPC), and Normalized Prediction Distribution Errors (NPDE).

#### 2.2.4 Results

Based on the report (Exposure-Efficacy Analyses of TCZ of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis), the indirect-response model with an inhibitory effect on DAS28 ‘production’ rate by TCZ serum concentrations was used to describe the magnitude and the time-course of DAS28 score reduction. The model supported the observation that the 8 mg/kg IV Q4W and 162 mg SC QW dosing regimens have similar efficacy. Both the 8 mg/kg IV Q4W and 162 mg SC QW dosing regimens are also more efficacious than the 162 mg SC Q2W dosing regimen.

Based on the final model, the population mean of the maximum effect of TCZ corresponds to 56.5% reduction of DAS28 from baseline. The relationship between TCZ concentration and DAS28 is independent of the route of administration (i.e., IV vs SC). No covariate was found to have a clinical impact on the effect of TCZ on DAS28.

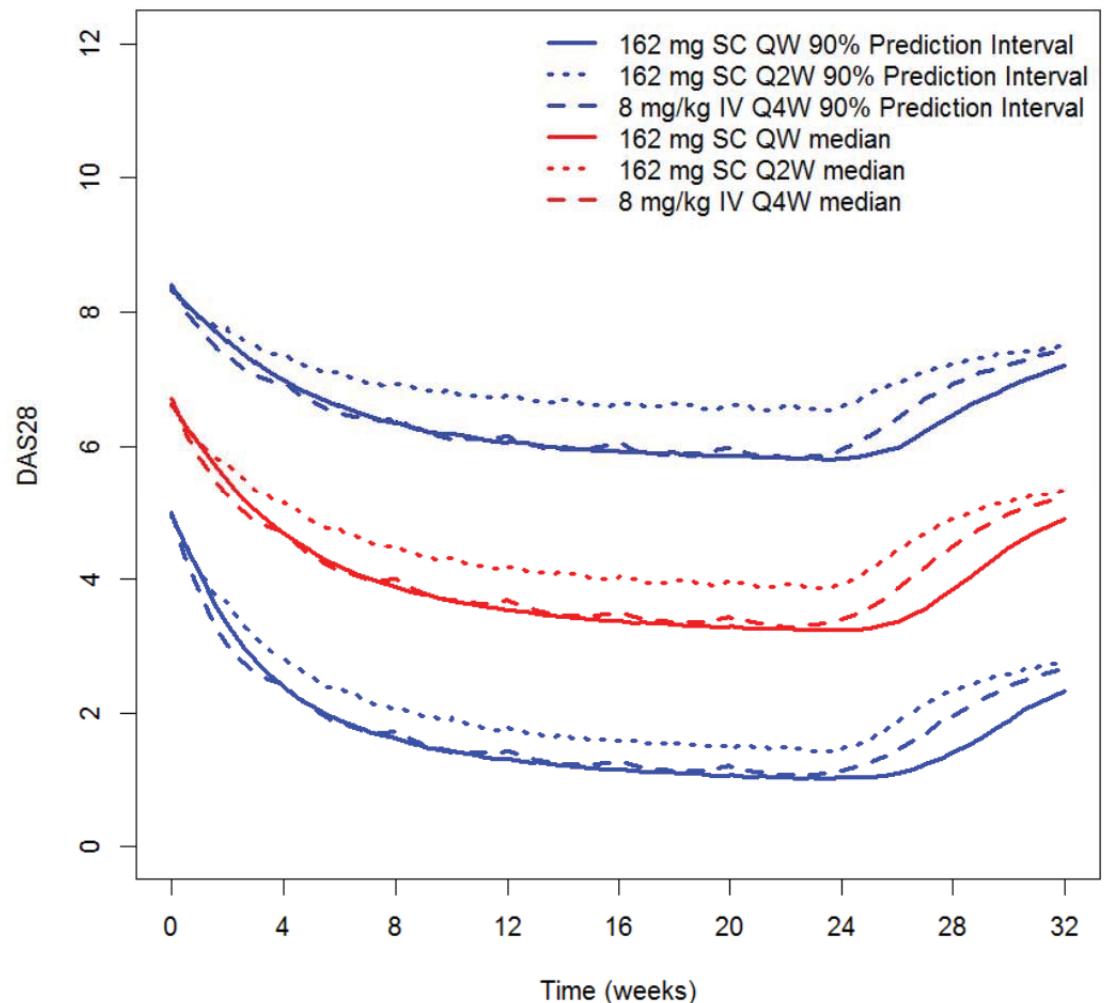
The covariates that remained in the final model are as follows: baseline values of CRP, HAQ, VASP, and PAIN for DAS28 values at baseline (BASE parameter) with positive relationships, which is in line with the fact that all these covariates are markers of RA disease activity; gender for the maximum effect of tocilizumab (Emax) with higher Emax in males; age and baseline IL6 for Emax with positive relationships. These findings are consistent with the exposure-efficacy response analysis conducted based on IV data. The final model passed the model evaluation assessment as described in previous section.

To evaluate the covariate effects on DAS28 response (gender, age, baseline CRP, and baseline IL6), simulations were performed to predict the time courses of DAS28 corresponding to different covariate levels. It was found that males and younger patients tended to have slightly lower DAS28 levels. Subjects with high baseline CRP tended to have significantly higher baseline DAS28 scores. However, the simulation results predicted that the difference in DAS28 levels for different baseline CRP groups disappeared after about 10 weeks of dosing for the 162 mg SC QW and 8 mg/kg IV Q4W regimens. In comparison, the DAS28 difference remained almost constant throughout the course of treatment for the 162 mg SC Q2W regimen. A slightly higher DAS28 scores was observed for subjects with higher IL6 levels but the DAS28 scores decreased to the same levels as in subjects with low baseline IL6 after 4-5 weeks for the 162 mg SC QW and 8 mg/kg IV Q4W regimens.

Overall, except for baseline CRP level for 162 mg SC Q2W regimen, the rest of covariate effects on DAS28 projections were found to be small based on sponsor's analysis.

Simulations were performed based on the final model for the DAS28 time-course for a 24 week treatment schedule. The simulated DAS28 profiles for three active treatments are shown in Figure 4. It showed that DAS28 scores steadily decrease after a rapid drop during the first 8 weeks. The responses to TCZ regimens of 8 mg/kg IV Q4W and 162 mg SC QW were comparable and the response was relatively smaller for 162 mg SC Q2W regimen.

Figure 4 Simulated DAS28 over Time, by Dosing Regimen.



Source: Figure 124 from report of Exposure-Efficacy Analyses of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

Note: Simulations were performed 100 times for each subject in the analysis dataset using subject's covariates, PK parameters, and nominal dosing.

*Reviewer's comment:*

The relationship between exposure ( $C_{trough}$ ) and efficacy response in terms of ACR responses were also evaluated separately. As shown in Table 4, ACR20/50/70 response rates was summarized by the four exposure quartiles for 8mg/kg IV, 162 mg SC QW and Q2W dose regimens. For the 162 mg Q2W SC treatment, there was an overall trend for an increase in the ACR response rate of any type with increased  $C_{trough}$ . For the QW SC treatment, similar pattern was observed for ACR20 response but with a lesser extent. In contrast, the response rates of ACR 50 and 70 seemed to reach plateau level after the second  $C_{trough}$  quartile. For the 8 mg/kg Q4W IV treatment, no clear trend toward a greater response with increasing Tocilizumab (BLA125472)

Page 13 of 27

exposure as measured by  $C_{\text{trough}}$  was observed. These findings indicate a clear exposure – efficacy response relationship for the 162 mg TCZ SC Q2W dosing.

Table 4 Patients with ACR responses at Week 24 by  $C_{\text{trough}}$  quartiles (ITT-PK Population) (Studies WA22762 & NA25220).

	NA25220 (162 mg TCZ SC q2w)				WA22762 (162 mg TCZ SC qw)				WA22762 (8 mg/kg TCV IV q4w)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number of patients	98	98	98	97	131	129	130	129	134	135	134	131
Mean $C_{\text{trough}}$ ( $\mu\text{g}/\text{mL}$ )	0.1	2.6	7.6	17.4	14.6	32.7	47.9	80.1	4.1	12.2	20.2	38.9
Median $C_{\text{trough}}$ ( $\mu\text{g}/\text{mL}$ )	0.1	2.4	7.5	16.5	15.4	33.1	47.7	72.5	4.1	12.0	19.8	36.9
ACR20 responders, n (%)	42 (43)	63 (64)	70 (71)	71 (73)	82 (63)	99 (76)	95 (73)	106 (82)	101 (75)	110 (81)	108 (81)	102 (78)
ACR50 responders, n (%)	24 (24)	40 (41)	48 (49)	50 (52)	51 (39)	67 (52)	69 (53)	69 (53)	78 (58)	69 (51)	77 (57)	59 (45)
ACR70 responders, n (%)	8 (8)	16 (16)	29 (30)	25 (26)	26 (20)	37 (28)	36 (28)	35 (27)	46 (34)	40 (30)	43 (32)	33 (25)

Q1-Q4 refer to the subgroups by  $C_{\text{trough}}$  exposure quartile (from lowest to highest  $C_{\text{trough}}$ ).

Source: Table 16 from report of Summary of Clinical Pharmacology

In the reviewer's opinion,  $C_{\text{trough}}$  cannot be used as a universal TCZ PK exposure measure for ACR response and it as a measure of drug exposure should be interpreted in combination with dosing frequency (i.e., SC Q2W, SC QW, or IV Q4W) and route of administration (i.e., IV vs. SC). As shown by Table 4, higher  $C_{\text{trough}}$  levels associated with a particular dosing frequency and/or route of administration could correspond to lower ACR responses compared to lower  $C_{\text{trough}}$  levels associated with other dosing frequencies and/or route of administration. For example, the mean Q3  $C_{\text{trough}}$  of 7.6  $\mu\text{g}/\text{ml}$  associated with TCZ SC Q2W and the mean Q1  $C_{\text{trough}}$  of 4.1  $\mu\text{g}/\text{ml}$  associated with TCZ IV Q4W were about 50% and 30% of the Q1  $C_{\text{trough}}$  of 14.6  $\mu\text{g}/\text{ml}$  associated with TCZ SC QW, respectively. However, the ACR responses associated with the Q3 exposure of SC Q2W and Q1 exposure of IV Q4W were significantly higher than ones associated with the Q1 exposure of SC QW. Therefore, TCZ  $C_{\text{trough}}$  only reflects the relative drug exposure within the same dosing frequency and dosing regimen. Caveat should be given when interpret  $C_{\text{trough}}$  as an overall PK exposure measure.

In the exposure-DAS28 response model, the contemporary TCZ serum concentration, instead of  $C_{\text{trough}}$ , is used as a dynamic PK exposure input as the efficacy driver. This is in line with the reviewer's opinion that  $C_{\text{trough}}$  cannot be used as a universal PK exposure measure for efficacy response.

The model predicted the main driver for DAS28 response is TCZ exposure and no other variables were identified as significant. Two key pieces of demographic information that the reviewer feels are important, body weight and region, were not evaluated during covariate model building.

As indicated in subgroup analyses in the study report, although the proportion of patients achieving an ACR20 response was similar between arms within the regions and body weight groups, ACR responses differed either between regions (i.e., North America, South America, Europe, and the rest of world) or between body weight groups (<60 kg, 60-100 kg, and  $\geq 100$  kg). Patients in the heaviest weight group ( $\geq 100$  kg) and/or patients from in North America had the lowest responses for both the 162 mg SC QW and the 8 mg/kg IV Q4W regimens (Table 5 and Table 6).

As shown in Table 5, a lower ACR20 response rate of 51% was observed in the  $\geq 100$  kg body weight group than the rates of 71-76% in the other two weight groups following the 8 mg/kg IV Q4W treatment regimen. It has been found that drug exposure of patients with high body weight was relatively higher than drug exposure of patients with low body weight following 8 mg/kg IV dosing (Table 3). The finding of relatively lower ACR20 response rate for patients weighting  $\geq 100$  kg following TCZ IV administration cannot be supported by lower drug exposure and is likely to be related to high body weight and/or geographic region. In addition, no strong collinearity relations were identified between body weight and other covariates such as baseline levels of CRP, Age, IL6, DAS28 that were evaluated in the model building process (Figure 5). Therefore, potential relationship between body weight and efficacy response cannot be fully assessed.

Taking all considerations into account, caveats should be given to interpret the exposure-efficacy response as proposed given high correlation between DAS28 and ACR20 scores. Future model refinement needs to assess the impact of body weight and/or region on the efficacy response.

Table 5 Percentage of ACR responders at Week 24 by weight: studies WA22762 and NA25220 vs. historical pooled IV Data (ITT population).

	Study WA22762		Study NA25220		Pooled IV Historical Data		
	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)
$\leq 80$ kg	(n = 144)	(n = 146)	(n = 119)	(n = 58)	(n = 377)	(n = 185)	(n = 286)
ACR20	74.3%	76.0%	63.0%	29.3%	63.7%	52.4%	23.4%
ACR50	50.0%	52.7%	43.7%	10.3%	37.7%	29.7%	8.7%
ACR70	23.6%	35.6%	23.5%	3.4%	19.9%	13.0%	2.1%
$80\text{--}<100$ kg	(n = 425)	(n = 422)	(n = 292)	(n = 150)	(n = 1073)	(n = 524)	(n = 773)
ACR20	68.0%	71.1%	62.0%	32.7%	56.9%	46.0%	24.5%
ACR50	45.6%	48.1%	40.8%	12.7%	36.0%	24.2%	8.5%
ACR70	25.2%	26.5%	19.5%	5.3%	17.4%	9.2%	1.9%
$\geq 100$ kg	(n = 62)	(n = 63)	(n = 26)	(n = 11)	(n = 120)	(n = 60)	(n = 105)
ACR20	50.0%	50.8%	38.5%	27.3%	53.3%	25.0%	18.1%
ACR50	33.9%	22.2%	11.5%	18.2%	33.3%	20%	10.5%
ACR70	12.9%	4.8%	3.8%	9.1%	15%	10%	4.8%

ACR = American College of Rheumatology; TCZ = tocilizumab; SC = subcutaneous; IV = Intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w / q4w = once every 2/4 weeks.

Source: WA22762:eteprsp01\_acrsp\_wgt\_24\_1; NA25220:eteprsp01\_acrsp\_wgt\_wk24\_1; Pooled 24- Week IV: etsumacrz20pool\_id003\_wk245; ACR50/70 for historical IV calculated from original filing outputs: etsumacrwgtwk24\_ah338\_pool\_70.rp8, etsumacrwgtwk24\_ah338\_pool\_50.rp8, etsumacrwgtwk24\_ah338\_062\_70.rp8, etsumacrwgtwk24\_ah338\_062\_50.rp8

Source: Table 36 from report of Summary of Clinical Efficacy

Table 6 Percentage of ACR 20 responders at Week 24 by geographic region: studies WA22762 and NA25220 vs. historical pooled IV data (ITT Population).

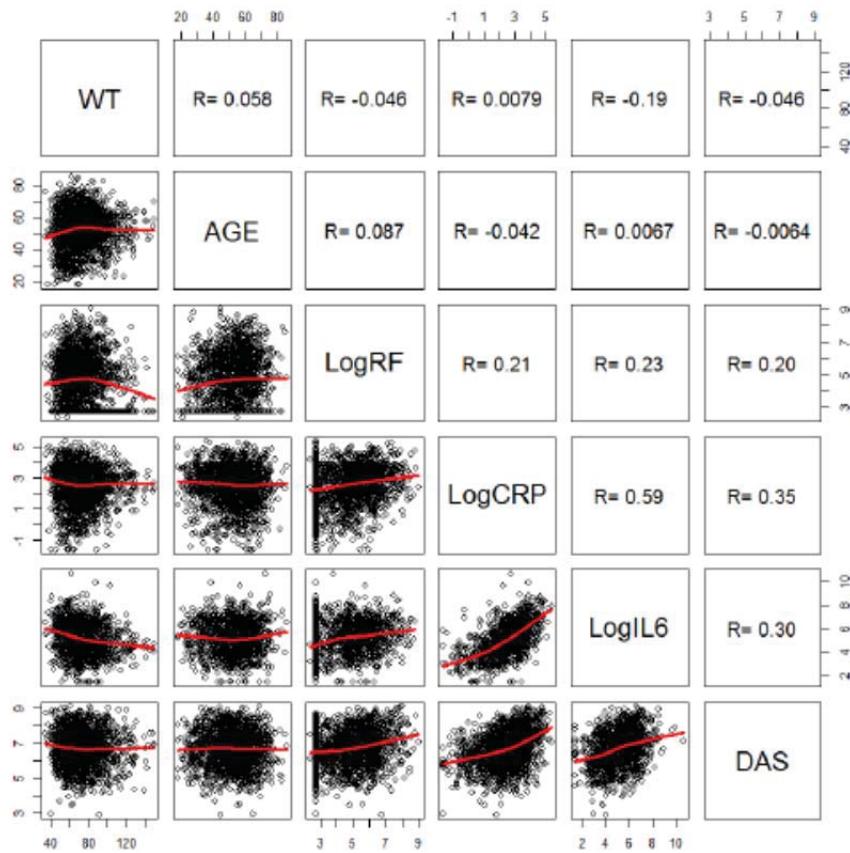
Region Category	Study WA22762		Study NA25220		Historical IV Data			
	TCZ 162 mg SC qw + DMARD (N = 631)	TCZ 8 mg/kg IV q4w + DMARD (N = 631)	TCZ 162 mg SC q2w + DMARD (N = 437)	Placebo SC q2w + DMARD (N = 219)	TCZ 8 mg/kg IV q4w + DMARD (N = 1576)	TCZ 4 mg/kg IV q4w + MTX (N = 773)	Placebo IV q4w + DMARD (N = 1168)	
North America	(n = 180) 47.8%	(n = 181) 55.2%	(n = 89) 38.2%	(n = 45) 15.6%	(n = 591) 47.5%	(n = 225) 36.4%	(n = 402) 20.4%	
South America	(n = 155) 74.2%	(n = 155) 79.4%	(n = 176) 65.3%	(n = 89) 36.0%	(n = 320) 69.1%	(n = 158) 57.0%	(n = 231) 35.9%	
Europe	(n = 199) 74.9%	(n = 198) 70.7%	(n = 101) 70.3%	(n = 49) 42.9%	(n = 500) 63.6%	(n = 314) 46.2%	(n = 417) 21.8%	
Rest of World	(n = 97) 79.4%	(n = 97) 82.5%	(n = 71) 64.8%	(n = 36) 25.0%	(n = 165) 58.8%	(n = 76) 47.4%	(n = 118) 17.8%	

ACR = American College of Rheumatology; TCZ = tocilizumab; SC = subcutaneous; IV = Intravenous; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; qw = once weekly; q2w / q4w = once every 2/4 weeks.

Source: WA22762:eteprsp01\_acrsp\_reg\_24\_1; NA25220:eteprsp01\_acrsp\_reg\_wk24\_1; Pooled 24-Week IV: etsumacr20pool\_id003\_wk244

Source: Table 41 from report of Summary of Clinical Efficacy

Figure 5 Correlation of continuous covariates.



Source: Figure 10 from report of Exposure-Efficacy Analyses of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

Note: The continuous covariates (points) and the red loess (local regression smoother) trend lines are plotted. Correlation coefficients between the covariates are also presented.

## 2.3 Exposure-safety (neutrophil counts, serious adverse events (SAE)) response analysis

### 2.3.1 Analysis Dataset

The dataset for exposure-safety response for population PK-neutrophil count analysis included dosing, neutrophil counts and covariate data from the Phase 3 studies WA22762 and NA25220. Only the data from the first 24-week dosing period of each study were included in the analysis. The number of subjects and observations in each study is shown in Table 7.

Table 7 Number of subjects and observations in each study.

<b>Study</b>	<b>Number of Subjects</b>	<b>Number of Observations Used in the Analysis</b>	<b>Number of Excluded Observations-Outliers</b>
WA22762	1250	10873	67
NA25220	637	4997	19
All Studies	1887	15870	86

Source: Table 7 from report of Exposure-Safety Analyses of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

### 2.3.2 Model building

#### 2.3.2.1 Exposure-response model for neutrophil counts

For the IV administration, the time-course of neutrophil counts was described by an indirect-response model with stimulation of elimination rate that was described by a sigmoidal function of TCZ serum concentration. An updated model was also used to describe the time-course of neutrophil counts following TCZ SC administration. The updated model combined an immediate direct effect (that affected all circulating neutrophils) with the slow effect described by the indirect response model (that affected only a fraction of the circulating neutrophils). During base model selection, prediction performance with the indirect-response model and the updated model were compared by visual inspection of diagnostic scatter plots, plausibility of the parameter estimates, precision of the parameter estimates, the minimum objective function value (OFV) and the number of estimated parameters. The difference in the OFV between hierarchical models is asymptotically  $\chi^2$  distributed with a degree of freedom equal to the difference in number of parameters between the two models in comparison. A p value of 0.001 for one additional parameter corresponds to a difference in the objective function of 10.83.

Full model with backward parameter elimination was used to establish the final covariate model. For full model, potential covariate-parameter relationships were identified based on scientific interest, mechanistic plausibility, knowledge gained from the previously developed model based on the IV data, and exploratory graphics. The full model did not simultaneously include effects of strongly correlated or collinear predictors. A similar backward elimination procedure to the one used for exposure-DAS28 response model was employed to derive the final covariate model. Please refer to section 2.2.2 for details.

#### 2.3.2.2 Graphical analysis of relationships between observed TCZ concentrations and Serious Adverse Events (SAE) and time course of main safety parameters

Graphical analyses were used to explore potential relationships between drug exposure and safety responses in terms of SAE and other safety parameters. The following SAEs were evaluated: any SAE, SAE of infections and infestations, SAE of gastrointestinal

disorders, SAE of cardiac disorders, SAE of neoplasms benign, malignant and unspecified (including cysts and polyps). The following safety parameters were evaluated: hematology (i.e., white blood cells, neutrophil, and platelets counts), biochemistry (i.e., total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, total protein, total cholesterol, cholesterol-HDL, cholesterol-LDL, and triglycerides)

Graphical analyses for potential relationships between TCZ concentration and SAE were carried out by highlighting the observed TCZ concentration profiles of SAE positive subjects from the pool of all individual observed TCZ concentration profiles for each SAE category, excluding subjects from study 25220 that escaped starting at week 12 (e.g. who switched from Q2W to QW regimen). Visual comparison was used to check whether SAE positive subjects were associated with higher overall drug concentrations when compared to the population pool.

Graphical analyses of the potential relationship between drug exposure and safety parameter responses were carried out by assessing the relationship between the observed values of the laboratory safety parameters and steady-state TCZ exposure ( $C_{trough}$ ).  $C_{trough}$  value was computed using individual subject's dosing history and the individual PK parameters from the final population PK model. Again, subjects from study 25220 that escaped at week 12 were excluded from the analysis. Equal number of subjects were assigned to low, medium, or high exposure categories based on  $C_{trough}$  values within each treatment regimen. For each safety parameter, the individual observed tocilizumab concentration profiles were also overlaid and compared for subjects in each of the three exposure categories by treatment, and separately for placebo subjects from study 25220.

### 2.3.3 Model evaluation

The model evaluation procedure for exposure-neutrophil count model is similar to the one used for exposure-DAS28 response model. Refer to section 2.2.3 for details.

### 2.3.4 Results

Overall, both models provided the excellent fit of the data. Therefore, the more parsimonious indirect-response model was selected both as the final base model and consequently the final model.

For covariate evaluations, it was found that higher neutrophil count at baseline (BASE) was associated with males, smokers, and subjects with higher baseline C-reactive protein (CRP). Emax increased with increasing IL6 level. Therefore, the full model included the effects of CRP, age, and sex on all parameters, IL6 on Emax, concentration to achieve 50% effect (EC50), and baseline neutrophil count, PCOR and smoking (SMK) on baseline neutrophil count, and previous treatment with corticosteroids (PCOR) on first order elimination rate (Kout). Post backward elimination, the retained covariates were: baseline CRP, PCOR, and SMK on BASE; age on kout; gender on EC50, and baseline CRP and IL6 concentrations on Emax.

Key parameters of the final model were estimated with reasonable precision for the structural parameters (relative standard error (RSE) = 1.2 - 7.7%), for the variances of the inter-individual random effects (RSE = 3.7 - 12%), for the residual error (RSE = 1%), for the covariate effects on BASE (RSE = 1.5-5.8%), and for the covariate effects on the other

parameters ( $RSE = 9.3 - 25.4\%$ ). In comparison, the inter-individual variability of the model parameters was high: 52.8%, 88.8%, and 152% for variances on  $Emax$ ,  $EC50$ , and  $k_{out}$ , respectively.

The final model passed all model evaluation criteria. Specifically, the predictive check evaluations (VPC, SVPC, PCS, and NPDE plots) showed that the model captured the central tendency and the inter-individual variability of neutrophil counts, as well as the identified relations between covariates and PK-PD parameters.

The magnitude of the covariate effects on model parameters is illustrated as in Table 8. The covariate effects on the neutrophil time course were also assessed using simulations. The covariates evaluated were gender, smoking, previous administration of corticosteroids, age, CRP, and IL6 for each dosing regimen. Overall, except for CRP on 162 mg following SC Q2W regimen, the effects of all the rest parameters on the neutrophil time profile did not seem to be clinically significant.

Based on the derived PK-PD model, rates of neutropenia for the three TCZ regimens following a 24-week dosing period and twice-a-week assessment for 32 weeks were simulated and the results are shown in Table 9. It was shown that the rates of neutropenia for all grades were lower for the 162 mg SC Q2W dosing regimen and were similar between 8 mg/kg IV Q4W and 162 mg SC QW regimens. More frequent sampling and high fluctuation of neutrophil counts due to high residual error led to higher than observed neutropenia rates.

Table 8 Covariate effects based on the final model.

Parameter	Covariate				Effect [95%CI] %
	Name (Unit)	Median [Range] or Level	Reference	Value	
BASE	CRP (mg/L)	13.5 [0.2 - 205]	10	1	-20.9 [-23; -18.8]
				100	26.3 [23.1; 29.9]
	PCOR	Previous corticosteroid therapy: Yes/No	No	Yes	22.9 [19.3; 26.4]
$k_{out}$	SMK	Non-smoker/ Smoker	Non-smoker	Smoker	17.5 [13.2; 21.9]
					-46.2 [-55.9; -34.3]
	Age (years)	54 [18 - 86]	50		37.4 [24.1; 52.1]
$EC_{50}$	Sex	Females/Males	Females	Males	-22 [-39.2; -4.7]
	CRP (mg/L)	13.5 [0.2 - 205]	10	1	-13.6 [-19.7; -7.1]
				100	15.7 [7.6; 24.5]
	Log(10*IL6 [pg/mL])	5.14 [1.39 - 10.7]	Log(10*20)	Log(10*1)	-42.5 [-48.1; -36.4]
				Log(10*10 <sup>3</sup> )	44.4 [35.1; 54.5]

Source: Table 23 from report of Exposure-Safety Analyses of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

Table 9 Simulated incidence of neutropenia (Grades 1 to 4) for each dosing regimen.

Dosing	Grade 1	Grade 2	Grade 3	Grade 4
162 mg qw SC	58.0% (1.9%)	47.3% (1.8%)	19.4% (1.5%)	2.08% (0.57%)
8 mg/kg q4w IV	57.7% (2.0%)	47.3% (1.9%)	19.0% (1.5%)	1.95% (0.51%)
162 mg q2w SC	40.8% (2.3%)	31.8% (2.3%)	11.5% (1.5%)	1.19% (0.51%)
Placebo	17.1% (2.5%)	11.4% (2.0%)	2.4% (1.0%)	0.39% (0.46%)

Source: Table 25 from report of Exposure-Safety Analyses of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis

Graphical exploration for potential relationship between drug exposure and SAE did not identify any prominent correlation. Overall, the occurrences of all types of SAEs were low (<5% for all SAE combined), and no pattern was found between the occurrence of SAEs of any categories (i.e., "Infections and Infestations", "Gastrointestinal disorders", "Cardiac Disorders", "Neoplasms benign, malignant and unspecified (including cysts and polyps)") and treatments based on sponsor's assessment. Subjects who experienced SAEs were not apparently associated with higher TCZ concentrations.

Safety parameters, which were graphically evaluated for potential relationships between exposure category in terms of Ctrough and time course patterns, included white blood cells, neutrophil counts, platelets, ALT, AST, total bilirubin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, serum albumin, and total protein.

For white blood cells and neutrophils, it was found that time to steady-state counts and the steady-state levels decreased with increasing exposure. For ALT, AST, total bilirubin, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides, slight increase in their levels over time were observed in all categories of exposure compared to the placebo group. However, no strong relationships between the increase and TCZ exposure or treatment regimen were identified. Similar patterns held for serum albumin levels with an exception that the combined data of the SC regimens seemed to show a slightly higher increase in the high exposure group compared to the low exposure group. For total protein, slight decrease over time was observed for all regimens including placebo and the decrease was not apparently related to drug exposure or treatment.

Overall, the hematological safety parameters demonstrated higher than placebo safety risk that approached plateau at high exposures. In general, potential hematology safety risks were similar between the 162 mg SC QW and 8 mg/kg IV Q4W regimens. For the 162 mg SC Q2W, it was associated with less safety parameter response and higher variability was observed across its associated exposure categories.

*Reviewers' analysis/comment:*

*Based on sponsor's safety report, the overall AE and infection rate was higher in the TCZ 162 mg QW SC treatment (study WA22762) than in the 162 mg Q2W SC treatment (study NA25220)(Table 10) , although there was a lack of exposure response relationship within each treatment regimen .*

Table 10 Rates of all AEs and infection AEs by observed Week 24 Ctrough quartiles (ITT - PK population for studies WA22762 and NA25220).

	NA25220 (162 mg TCZ SC q2w)				WA22762 (162 mg TCZ SC qw)				WA22762 (8 mg/kg TCV IV q4w)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number of patients	81	80	80	80	131	129	130	129	134	135	134	131
Mean C <sub>trough</sub> (μg/mL)	0.2	3.5	8.2	17.9	14.8	32.7	47.9	80.1	4.1	12.2	20.2	38.9
Median C <sub>trough</sub> (μg/mL)	0.1	3.6	8.1	16.6	15.4	33.0	47.7	72.5	4.1	12.0	19.8	36.9
Total Patient Years	37.5	37.0	37.1	37.0	63.3	62.1	62.6	62.2	64.7	65.0	64.7	63.3
Number of all AEs	177	136	139	158	388	292	373	346	349	345	367	356
AEs per 100 Patient Years	472	367	375	427	613	471	596	556	539	531	567	563
(95% CI)	(405- 547)	(308- 434)	(315- 442)	(363- 499)	(553- 877)	(418- 528)	(537- 618)	(499- 600)	(484- 599)	(476- 590)	(510- 628)	(506-624)
Number of Infections and infestations	40	30	25	26	68	62	75	72	61	80	76	78
Infection AEs per 100 Patient Years	107	81	67	70	107	100	120	116	94	123	117	123
(95% CI)	(76-145)	(55-118)	(44-99)	(46-103)	(83-136)	(77-128)	(94-150)	(91- 146)	(72-121)	(98-153)	(93-147)	(97-154)

Q1-Q4 refer to the subgroups by C<sub>trough</sub> exposure quartile (from lowest to highest C<sub>trough</sub>).

Source: Table 20 from report of Summary of Clinical Pharmacology

*The protocols for both pivotal studies WA22762 and NA25220 allowed for dose interruption of an infusion, skipping a dose, or dose reduction for the management of AEs (e.g., opportunistic infections and serious infections, GI perforations, demyelinating disorders, hematologic abnormalities and bleeding events, elevated liver enzymes, cardiovascular events and elevated lipids, malignancies, local ISRs, and hypersensitivity or anaphylaxis after SC injection). The most commonly reported system organ classes (SOCs) with AEs leading to dose modification included Infections and Infestations.*

*As shown by Table 11, it was found that the incidence of AEs leading to a dose modification/interruption either at Week 24 or at the clinical cutoff was significantly higher for 162 mg QW SC treatment (study WA22762) than for 162 mg Q2W SC treatment (Study NA25220: 36.1% vs. 16.7%). In comparison, the incidence was comparable between 162 QW SC and 8 mg/kg IV treatment (study WA22762: 36.1% for SC vs. 30.7% for IV).*

Table 11 Overview of AEs Leading to Dose Modifications/ Interruptions in Studies WA22762 and NA25220 until Clinical Cutoff (Safety Population).

	WA22762 162 mg SC TCZ qw (PFS) + DMARD N = 631	NA25220 8 mg/kg IV TCZ q4w + DMARD N = 631	NA25220 162 mg SC TCZ q2w (PFS) + DMARD N = 437
Total duration in study (PY)	454.20	401.02	222.09
Patients with AE	228 (36.1%)	194 (30.7 %)	73 (16.7 %)
Number of AEs	412	294	98
AEs per 100 PY	96.87 (95% CI) (88.03, 106.36)	78.0 (70.35, 87.98)	46.38 (37.85, 56.25)

AE = AE; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug;  
IV = intravenous; PFS = prefilled syringe; PY = patient years; q2w = every two weeks;  
q4w = every four weeks; qw = every week; SC = subcutaneous; TCZ = tocilizumab.

Clinical cutoff 16 January 2012 for WA22762 and 28 May 2012 for NA25220.

SC TCZ arms: Analyses include all patients who received SC TCZ using the PFS in the double-blind period starting from their first dose. Data after switch to IV TCZ (in WA22762) or the AI (in NA25220) in the open-label extension are not included.

IV TCZ arm: Analyses include all patients who received IV TCZ in the double-blind period starting from their first dose. Data after switch to SC TCZ in the open-label extension are not included.

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

Source: stae11\_dm\_b LTE CSR WA22762, stae11\_dm\_b CSR LTE NA25220

Source: Table 29 from report of Summary of Clinical Safety

*Consistent with IV TCZ treatment as well as characterized by the exposure-neutrophil count model, SC administration of TCZ induced an exposure/dose-dependent decrease in neutrophil counts. As observed in study WA22762, the rates for Grade 1 or 2 neutropenia for SC TCZ QW and IV Q4W regimens were comparable with Week 24 IV TCZ data at Week 24. Although the incidence of Grade 3 or 4 neutropenia at Week 24 was low and balanced across SC TCZ and IV TCZ dosing regimens, no evaluation has been reported whether this was attributable to dose modification or interruption due to safety events.*

*Based on the exposure-neutrophil count model simulations, the safety risk for grades 1-4 neutropenia was the lowest in the 162 mg Q2W SC treatment among all the evaluated active treatment regimens (i.e., 162 mg QW SC, 162 mg Q2W SC, and 8 mg/kg Q4W IV). The neutropenia risk was almost doubled in the 162 mg QW SC and 8 mg/kg Q4W IV treatment regimens compared to the 162 Q2W SC treatment regimen (19% vs 12% for grade 3, and 2.0% vs 1.2% for grade 4). The simulated trend is consistent with the observed trend as summarized in Table 12 in the intent to treat (ITT) PK population for grades 1&2 neutropenia incidence. It was also found the incidence of thrombocytopenia and ALT elevation was also lowest in the 162 mg Q2W SC treatment among the three active treatments.*

Table 12 Patients with laboratory abnormalities (worst value from normal at baseline) by observed Week 24 Cthrough quartiles (ITT - PK Population for Studies WA22762 and NA25220).

	NA25220 (162 mg TCZ SC q2w)				WA22762 (162 mg TCZ SC qw)				WA22762 (8 mg/kg TCV IV q4w)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number of patients	~81	~80	~80	~80	~131	~129	~130	~129	~134	~135	~134	~131
Mean $C_{trough}$ ( $\mu\text{g}/\text{mL}$ )	0.2	3.5	8.2	17.9	14.6	32.7	47.9	80.1	4.1	12.2	20.2	38.9
Median $C_{trough}$ ( $\mu\text{g}/\text{mL}$ )	0.1	3.6	8.1	16.6	15.4	33.0	47.7	72.5	4.1	12.0	19.8	36.9
Neutropenia Grade 1 (%)	5 (6)	3 (4)	12 (15)	18 (23)	20 (15)	24 (19)	33 (26)	26 (20)	14 (11)	20 (15)	22 (16)	21 (16)
Neutropenia Grade 2 (%)	0 (0)	4 (5)	5 (6)	9 (11)	9 (7)	17 (13)	12 (9)	27 (21)	5 (4)	9 (7)	19 (14)	17 (13)
Neutropenia Grade 3 (%)	1 (1)	2 (3)	4 (5)	1 (1)	1 (1)	2 (2)	5 (4)	2 (2)	3 (2)	2 (2)	3 (2)	7 (5)
Thrombocytopenia Grade 1 (%)	5 (6)	7 (9)	7 (9)	6 (8)	7 (5)	10 (8)	13 (10)	10 (8)	15 (11)	6 (4)	12 (9)	14 (11)
Thrombocytopenia Grade 2 (%)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Thrombocytopenia Grade 3 (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
ALT Elevation Grade 1 (%)	24 (31)	28 (38)	32 (44)	30 (38)	69 (59)	59 (50)	68 (57)	49 (40)	55 (45)	52 (44)	65 (50)	44 (37)
ALT Elevation Grade 2 (%)	1 (1)	3 (4)	2 (3)	0 (0)	4 (3)	8 (7)	4 (3)	1 (1)	5 (4)	5 (4)	5 (4)	4 (3)
ALT Elevation Grade 3 (%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	1 (1)	0 (0)	2 (2)	1 (1)	0 (0)	0 (0)

Q1-Q4 refer to the subgroups by  $C_{trough}$  exposure quartile (from lowest to highest  $C_{trough}$ ).

Note: Neutropenia Grade 4 was not observed in this analysis.

Source: Table 19 from report of Summary of Clinical Pharmacology

*Although the sponsor failed to identify a relationship between TCZ exposure and SAE incidence, the graphical analyses for potential relationship between drug exposure and SAE were mainly based on visual assessment and may be potentially involving subjective judgment. A reference to clinical safety review needed for an overall evaluation.*

#### Reviewer's overall comments:

*In conclusion, TCZ 162 mg SC QW and 8 mg/kg IV Q4W treatment regimens demonstrated comparable efficacy. The TCZ 162 SC Q2W dosing regimen also showed clinically superior efficacy improvements to placebo. However, the efficacy effect is less pronounced in > 100 kg weight group for 162 kg SC Q2W treatment compared to 162 kg SC QW and 8 mg/kg IV Q4W treatments (50.0%, 50.8%, 38.5%, and 27.3% for 162 mg SC QW, 162 mg SC Q2W, 8 mg/kg IV Q4W, and placebo in terms of ACR20 responses, respectively, at Week 24 in ITT population). By directly comparing the ACR20 responses of patients weighting > 100 kg between SC QW and SC Q2W treatments (i.e., 50% vs. 38.2%), the decreased ACR responses for 162 mg SC Q2W treatment is likely to be associated with less drug exposure. In addition, it was reported that a substantial % of escape patients who escalated from the Q2W SC regimen to the QW SC regimen showed an improvement in efficacy. Therefore, dose escalation from SCQ2W to SC QW for patients weighting > 100 kg to gain therapeutic advantage is reasonable.*

*Clinical data supported the starting dosing regimen of 162 mg SC Q2W for patients weighing < 100 kg, mainly based on four reasons. First, the efficacy response in terms of ACR20 were observed to be >60% for both SC QW and SC Q2W regimens for patients weighting < 100 kg. Second, higher safety risk were observed across studies for SC QW than for SC Q2W in terms of % of patients with any AE and grades 1 & 2 neutropenia. The exposure –safety model also predicted higher grades 3 & 4 neutropenia risk for QW regimen. Third, overview of AEs leading to dose modifications/ interruptions in studies WA22762 and NA25220 until Week 24 or clinical cutoff in safety population showed that the incidence of such events is higher in the SC QW treatment than in the SC Q2W treatment (27.3% vs. 13.5% at Week 24 and 36.1% vs. 16.7% at clinical cutoff). Starting from SC Q2W regimen lends the opportunity to patients for tolerance to TCZ regimen and has the advantage of less dose modifications/interruptions. Fourth, the*

*approved IV dosing regimen also recommends starting from a low dose of 4 mg/kg Q4W that can be escalated to 8 mg/kg Q4W based on clinical response.*

**Proposed labeling statements**

See clinical pharmacology review.

**Table 13. Analysis Data Sets/Reports**

Study Number	Name	Link to EDR
poppk.pdf	Population PK Analysis of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\53-clin-stud-rep\533rep-human-pk-stud\5335-popul-pk-stud-rep\wa22762-na25220-pk\poppk.pdf
poppk-efficacy.pdf	Exposure-Efficacy Analyses of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\53-clin-stud-rep\533rep-human-pk-stud\5335-popul-pk-stud-rep\wa22762-na25220-pk\poppk-efficacy.pdf
poppk-safety.pdf	Exposure-Safety Analyses of Tocilizumab of Phase III Studies WA22762 and NA25220 in Rheumatoid Arthritis	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\53-clin-stud-rep\533rep-human-pk-stud\5335-popul-pk-stud-rep\wa22762-na25220-pk\poppk-safety.pdf

### 3 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Link to EDR
317-ctl	Population pharmacokinetic model (Final)	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\datasets\wa22762-na25220-pk\analysis\programs\317-ctl.txt
317-lst	Output of final population pharmacokinetic model	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\datasets\wa22762-na25220-pk\analysis\programs\317-lst.txt
630-ctl	Final model for exposure-DAS28 response analysis	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\datasets\wa22762-na25220-pk\analysis\programs\630-ctl.txt
630-lst	Output of Final model for exposure-DAS28 response analysis	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\datasets\wa22762-na25220-pk\analysis\programs\630-lst.txt
226-ctl	Final model for exposure-neutrophil count analysis	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\datasets\wa22762-na25220-pk\analysis\programs\246-ctl.txt
246-lst	Output of exposure-neutrophil count final model	\cdsesub1\bla\ectd_submissions\stn125472\0000\m5\datasets\wa22762-na25220-pk\analysis\programs\246-lst.txt

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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LIANG ZHAO  
09/16/2013

SATJIT S BRAR  
09/16/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

**General Information About the Submission**

	Information		Information				
NDA/BLA Number	BLA125472	Brand Name	Actemra®				
OCP Division (I, II, III, IV, V)	II	Generic Name	Tocilizumab				
Medical Division	570	Drug Class	Anti-human IL-6 receptor mAb				
OCP Reviewer	Liang Zhao, Ph.D.	Indication(s)	RA				
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Prefilled Syringe (PFS) for subcutaneous administration				
Pharmacometrics Reviewer	Liang Zhao, Ph.D.	Dosing Regimen	<p>Recommended Adult Subcutaneous (SC) Dosage:</p> <table border="1" style="margin-left: 20px;"> <tr> <td>Patients less than 100kg weight</td> <td>162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response</td> </tr> <tr> <td>Patients at or above 100kg weight</td> <td>162 mg administered subcutaneously every week</td> </tr> </table>	Patients less than 100kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response	Patients at or above 100kg weight	162 mg administered subcutaneously every week
Patients less than 100kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response						
Patients at or above 100kg weight	162 mg administered subcutaneously every week						
Date of Submission	December 21 <sup>st</sup> , 2012	Route of Administration	Subcutaneous injection				
Estimated Due Date of OCP Review	August 10 <sup>th</sup> , 2013	Sponsor	Genentech, Inc. A Member of the Roche Group				
Medical Division Due Date		Priority Classification	Standard				
PDUFA Due Date	October 21 <sup>st</sup> 2013						

*Clin. Pharm. and Biopharm. Information*

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		EIA and ELISA methods
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	6		WP18097, BP22065, NP25539, BP21894, NP22623, MRA227JP
<b>Healthy Volunteers-</b>				
single dose:	X	4		WP18097, BP22065, NP25539, BP21894
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:	X	2		NP22623, MRA227JP
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA 125472

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>	X	6		WP18097, BP22065, NP25539, BP21894, NP22623, MRA227JP
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>	X	3		Based on data from two phase III studies, WA22762 and NA25220
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>	X	2		WP18097, BP22065
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>	X	1		NP25539
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				Request for deferral of submission of pediatric information
<b>Literature References</b>				
<b>Total Number of Studies</b>		8		

On initial review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of	X			

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA  
125472

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	the analytical assay?			
5	Has a rationale for dose selection been submitted?	X		
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X		
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X		
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X		

**Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)**

<b>Data</b>				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X		
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x	
<b>Studies and Analyses</b>				
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
<b>General</b>				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

Yes

*This BLA supplement submission (BLA125,472) is filable from a Clinical Pharmacology standpoint. Please refer to the attached slides as presented in filing meeting for details.*

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA 125472

# **CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.



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## **Conclusions and Mid-cycle Deliverables**

- Fileable from a clinical pharmacology perspective
  - Relevant datasets (i.e., for PK, PD, and immunogenicity) are included in submission
- Mid-cycle deliverables:
  - Review of popPK analysis
  - Label review of clin-pharm relevant info

January 23rd, 2013

BLA 125472: Torcilitzumab

1



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## **PK Information in Submission**

- Absolute BA:
  - WP18097: 56.5%
  - BP22065: 48.8%
- Reach Steady State at ~ Week 12-15
- More than proportional increase in exposure
- Lower exposure with higher body weight for SC
- IM status generally does not impact PK
- Half lives:
  - 12-13 days for 162 mg QW SC;
  - 1.8-4.9 days for 162 mg Q2W SC;
  - 6.6-18.6 days for 8 mg/kg Q4W IV

January 23rd, 2013

BLA 125472: Torcilitzumab

2

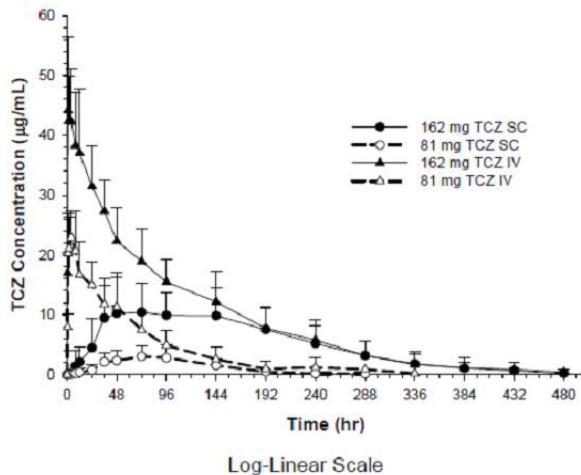
# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement



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## IV and SC PK Profile Comparison Study BP22065



January 23rd, 2013

BLA 125472: Torcizumab

3



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

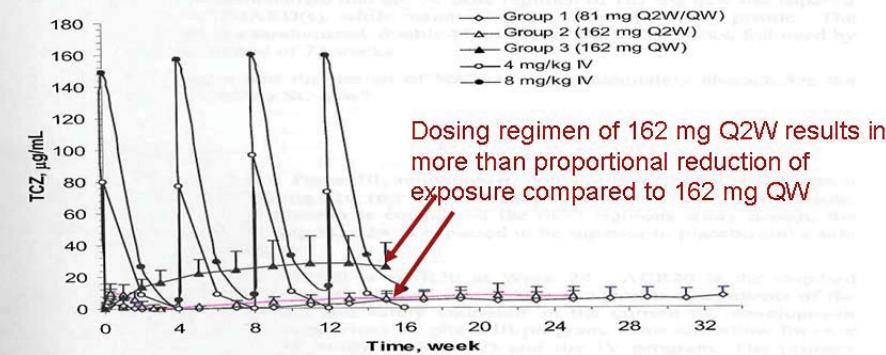
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## PK Profiles for Different Regimens

(Figure adapted from IND11972, May 2010)

Figure 5

Mean  $\pm$  SD Serum TCZ Concentrations Following Administration of 162 mg SC QW and Q2W in Study MRA227 and 4 and 8 mg/kg IV Q4W in Study LRO301



Key: Group 1 (N=8 up to week 11 and N=7 thereafter): patients received 81 mg SC single dose at week 1, started Q2W dosing at week 3, and switched to Q2W dosing at week 9; Group 2 (162 mg Q2W, N=12): patients received single 162 mg SC dose at week 1 and started Q2W dosing at week 3; Group 3 (162 mg QW, N=12): patients received 162 mg QW dosing for 15 weeks until the date-cut of Sept 2009 [4]. PK profiles from 4 and 8 mg/kg IV infusion every 4 weeks in RA patients in the Phase 2 dose-finding study LRO301 are illustrated for comparison [7]. LRO301 was selected for comparison as PK from phase 2 and

January 23rd, 2013

BLA 125472: Torcizumab

4

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement



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## Dose Selection

- Chosen on the basis of PK, PD, and safety data from two Phase I/II studies (MRA227JP and NP22623) in RA patients
  - TCZ SC dose regimens of 81 mg and 162 mg q2w/qw were tested
- PD profiles (CRP, ESR, and sIL-6R) of the TCZ SC 162 mg QW regimen were found to be most comparable to the TCZ IV 8 mg/kg dosing regimen
- Dose regimen of 162 mg SC Q2W also increased levels of the sIL-6R-TCZ complex, achieved CRP normalization, and resulted in an ESR reduction from baseline
  - Despite being slower and less pronounced compared with the 162 mg qw dose regimen, the PD responses with the 162 mg q2w regimen were superior to the lower SC doses tested (81 mg q2w/qw)

January 23rd, 2013

BLA 125472: Tocilizumab

5

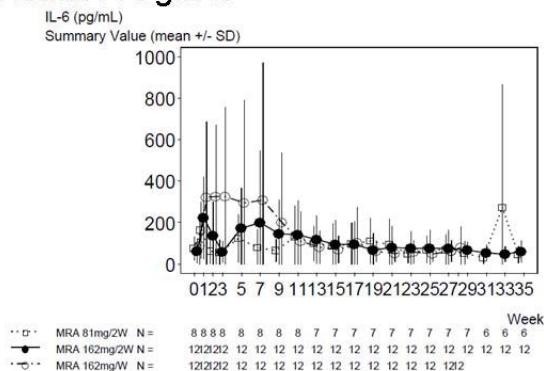


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## Summary of PD

- Serum concentrations of IL-6, sIL-6R, CRP, ESR were summarized graphically and descriptively
- Studies conducted in both healthy volunteers and RA patients
- Representative figure:



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6

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## **Overview of PK-PD studies Providing PK Data**

- A total of 9 clinical studies of TCZ (SC or IV)
- PopPK, exposure-efficacy and exposure-safety analyses are based on pooled data from the pivotal Phase III studies WA22762 and NA25220

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7



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## **PopPK Analysis of Phase III Data**

- Phase III studies: WA22762 and NA25220
- Two cpt model with parallel linear/nonlinear eliminations
- Statistically significant covariates identified:
  - Body weight and HDL-cholesterol on CL
  - Body weight, total protein, and albumin on Volume of distribution
  - Normalized creatinine clearance on Vm
  - Age and study on absorption rate
  - Injection site on BA
- Covariates with appreciable effect
  - Body weight on CL (~70-80% difference in CL in body weight range) and Volume of distribution

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8

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### **Sponsor Analyses of Exposure-Efficacy Relationship Using Phase III Data**

- Data construction: WA22762 & NA25220
- Quartile and graphical analyses of the relationship between TCZ exposure and the main efficacy and PD parameters and modeling of exposure versus DAS28
- Results: Efficacy similar between 162 QW SC and 8 mg/kg Q4W IV
- Relationship not dependent on ROA?

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9



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### **Bioanalytical Issues**

- No key concerns have been found. All the analytical methods and validation reports were in or crossed referenced to the original submission.

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10

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**Labeling Additions Pertaining to  
Clinical Pharmacology**

- Section 6.2: Immunogenicity
- Section 12.3 Pharmacokinetics  
Rheumatoid Arthritis—Subcutaneous  
Administration

January 23rd, 2013

BLA 125472: Torcilizumab

11

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/s/

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LIANG ZHAO  
01/29/2013

SURESH DODDAPANENI  
01/29/2013