CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

BLA	STN 125276
Submission Dates:	7/7/2008; 7/17/2008; 8/7/2008 Amendments
Brand Name	ACTEMRA®
Generic Name	Tocilizumab (RO4877533 or myeloma receptor antibody), recombinant humanized anti-human monoclonal antibody
OCP Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Sponsor	Roche Pharmaceuticals
Relevant IND	BB-IND 11,972
Submission Type; Code	NME; 1S
Formulation; Strength(s); Administration Route	Concentrate solution; 20 mg/mL; Intravenous infusion
Proposed Indication	Indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who are naïve to treatment with, or who had an inadequate response to, one or more DMARDs or TNF antagonists. ACTEMRA can be used alone or in combination with methotrexate or other DMARDs
Proposed Dosage Regimen	The recommended dose of ACTEMRA for adult patients with rheumatoid arthritis is 8 mg/kg given once every 4 weeks as a 60-minute single intravenous drip infusion

Table of Content

Executive Summary

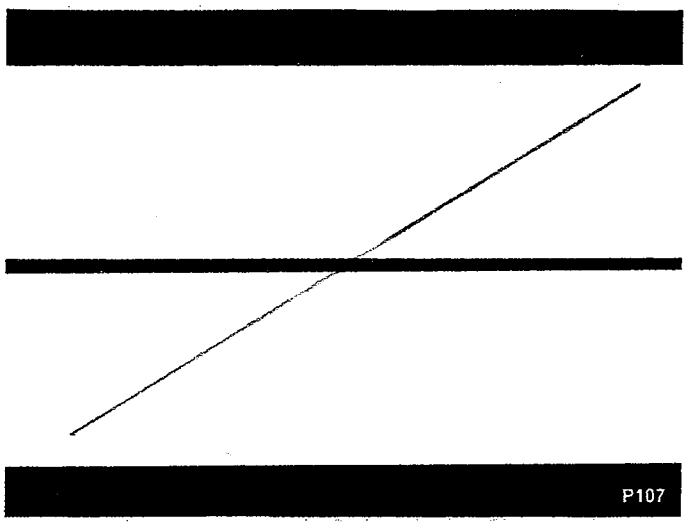
The Clinical Pharmacology review for original BLA 125276 was signed off on July 28, 2008. This addendum includes the final labeling recommendation (Appendix 1) based on Sponsor's new proposed labeling received on July 17, 2008 and our review of Study WP18663 that was submitted to BB-IND 11972 and cross-referenced to this BLA on July 7, 2008. The review for Study WP18663 (entitled "*A multi-center, open-label, randomized, drug interaction study to investigate the pharmacokinetics of simvastatin (a substrate for CYP3A4) and methotrexate (MTX) in combination with tocilizumab (TCZ) in rheumatoid arthritis patients*") was signed off in DARRTS on August 11, 2008 and is attached to this addendum as Appendix 2.

Results from Study WP18663 showed that tocilizumab significantly affected PK of simvastatin and its metabolite, simvastain acid. Namely, exposure of simvastatin decreased 60%, one week following a single dose of 10 mg/kg of tocilizumab in RA patients. However, the levels were still slightly higher than those observed in healthy subjects indicating that efficacy may not be compromised in the presence of tocilizumab.

During the clinical studies, it was found that tocilizumab increased lipid levels in patients and lipid lowering agents including statins were coadministered. At the AC meeting, the Sponsor

b(4)

An information request was sent to the Sponsor to indicate what agents were used and how many patients were on each agent. (*Reviewer's Note: The Sponsor corrected the title from "Stain Therapy" to "Lipid Lowering Therapy".*)



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In the August 7, 2008 amendment submission, the Sponsor stated that "Of the 180 pts represented on slide P107 who were receiving lipid lowering agents, 134 were on statins alone

and an additional 13 were on a statin plus an additional lipid lowering agent." They also provided the following table (Table 1).

Atovastatin, simvastatin and lovastatin are metabolized by CYP3A4. Together, they accounted for > 65% lipid-lowering agent use. Because data showed that overall, these agents effectively loweried cholesterol levels in RA patients receiving tocilizumab, it appears that even though tocilizumab would affect PK of lipid-lowering drugs that are P450 substrates, tocilizumab may not negatively impact the efficacy of these agents.

Table 1. Summary of Concomitant Lipid Lowering Agents for Patients with a Pre and Post LDL result by Trial Treatment, Class and Preferred Term (Safety Population).

Class/ Other Treatment or Procedure	Pooled MRA N = 180 No. (%)
ALL CLASSES	
Total Pts with at Least one Treatment	180 (100)
Total Number of Treatments	217
STATINS	
Total Pts With at Least one Treatment	134 (74)
ATORVASTATIN	68 (38)
SIMVASTATIN	43 (24)
ROSUVASTATIN	20 (11)
LOVASTATIN	10 (6)
PRAVASTATIN	9 (5)
FLUVASTATIN	1 (<1)
Total Number of Treatments	151
FIBRATES	
Total Pts With at Least one Treatment	29 (16)
BEZAFIBRATE	15 (8)
FENOFIBRATE	11 (6)
GEMFIBROZIL	4 (2)
Total Number of Treatments	30
LIPID REGULATING AGENTS	
Total Pts With at Least one Treatment	22 (12)
EZETIMIBE	12 (7)
EZETIMIBE/SIMVASTATIN	9 (5)
COLESEVELAM HCL	1 (<1)
LOVASTATIN/NICOTINIC ACID	1 (<1)
Total Number of Treatments	23
SUPPLEMENTS	
Total Pts With at Least one Treatment	8 (4)
OMEGA-3 TRIGLYCERIDES	8 (4)
Total Number of Treatments	8
MISCELLANEOUS CARDIOVASCULAR AGENTS	
Total Pts With at Least one Treatment	3 (2)
AMLODIPINE/ATORVASTATIN	3 (2)
Total Number of Treatments	3
ION EXCHANGE RESINS	
Total Pts With at Least one Treatment	2 (1)
COLESTYRAMINE	2 (1)
Total Number of Treatments	2

Percentages are based on N.
Multiple occurrences of the same treatment in one individual counted only once.

Recommendation

The recommendation made in the Clinical Pharmacology review still stands. The labeling language is updated based on the results of Study WP18663.

Lei Zhang 8/21/08

Lei Zhang, Ph.D.

Concurrence: 8/21/08

Suresh Doddapaneni, Ph.D

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

Appendix 2. Review of Study WP18663.

Clinical Pharmacology Review

BB-IND:	11,972 ———	**Submission Date:**	7/7/2008
Product:	ACTEMRA® (Tocilizumab)	**Reviewer:**	Lei Zhang, Ph.D.
Sponsor:	Roche Palo Alto, CA	**Type of Submission:**	Final Clinical Study Report (No. 1029417)
		Review Date:	8/6/2008

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BB-IND 11,972-603

Tocilizumab (RO4877533, TCZ) is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G_1 (IgG_1) sub-class directed against the soluble and membrane-bound interleukin 6 receptor (IL-6R). The Sponsor submitted an original BLA (125276) for tocilizumab for the indication of RA on November 19, 2007.

At the time of BLA submission, drug interaction study WP18663, was on-going. The Sponsor submitted the final study report for this drug interaction study to BB-IND 11,972 and made a cross-reference to the BLA 125276.

Clinical Pharmacology review for BLA 1252776 was signed off on July 28, 2008. The review for this study will be attached as an addendum.

Review of Study WP18663:

Title: Research Report No. 1029417 (Study WP18663): A multi-center, open-label, randomized, drug interaction study to investigate the pharmacokinetics of simvastatin (a substrate for CYP3A4) and methotrexate (MTX) in combination with tocilizumab (TCZ) in rheumatoid arthritis patients

Study Period: January 23, 2006 to November 9, 2007
Study Sites: Multiple sites in the U.S.

INVESTIGATORS / CENTERS AND COUNTRIES

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Objective: To investigate the pharmacokinetics of simvastatin (a substrate for CYP3A4) and methotrexate (MTX) in combination with tocilizumab in rheumatoid arthritis patients.

Study Rationale: IL-6 is reported to inhibit the expression of cytochrome P450 (CYP). The results of an *in vitro* study (Study ADM 03-0155) suggested that the levels of expression of several P450 enzymes are affected when IL-6 signal transduction is inhibited with CYP3A4 being the most sensitive. The decreased P450 expression in the presence of IL-6 is completely reversed by 250 μg/mL tocilizumab, a concentration which can be attained following an 8 mg/kg infusion.

IL-6 levels are elevated in RA patients, typically about 40 pg/mL compared to only 4 pg/mL or less in healthy subjects. *(Reviewer's Note: IL-6 levels in RA patients are variable. For example, in Study LRO300 it was determined to be 3.2 to 923.6 ng/mL.)* If the *in vitro* down-regulation of cytochrome P450 by IL-6 were also to occur *in vivo*, the production of CYP3A4 would be reduced and exposure to drugs cleared by it would be raised. Since CYP3A4 is the most important drug-metabolizing isoform of cytochrome P450, the consequences could be of clinical relevance. For example, one might expect levels of simvastatin, a specific CYP3A4 substrate, to be higher in RA patients (with their high IL-6 levels) than normal patients. Administration of tocilizumab could normalize the P450 levels and result in elevated CYP3A4 and reduced cholesterol-lowering efficacy. Thus the effect would be similar to enzyme induction. However, it is not possible to predict the clinical significance of either putative IL-6-mediated down-regulation of CYP3A4 or any reversal of such an effect by tocilizumab. It is, therefore, necessary to carry out a clinical pharmacokinetic study to examine this possibility.

In addition, statins are very likely to be coadministered TCZ in RA patients to treat the lipid increasing effect observed with TCZ administration.

The effect of TCZ on the pharmacokinetics of MTX has not been studied. Since a high proportion of RA patients take MTX, it thus seemed reasonable to study effect of TCZ on PK of MTX.

Dose Selection: If IL-6 does down-regulate CYP3A4 *in vivo*, the greatest reversal of the effect will be with a dose of TCZ known to consistently and maximally suppress IL-6R signaling, as indicated by normalization of CRP. The general recommended clinical dose of TCZ is 8 mg/kg every 4 weeks in RA patients. Therefore, in this study the TCZ dose for the single-dose IV administration will be 10 mg/kg to mimic the TCZ exposure (AUC, Cmax) at steady-state following 8 mg/kg every 4 weeks in RA patients. A single dose of 10 mg/kg was expected to be well tolerated and safe in RA patients.

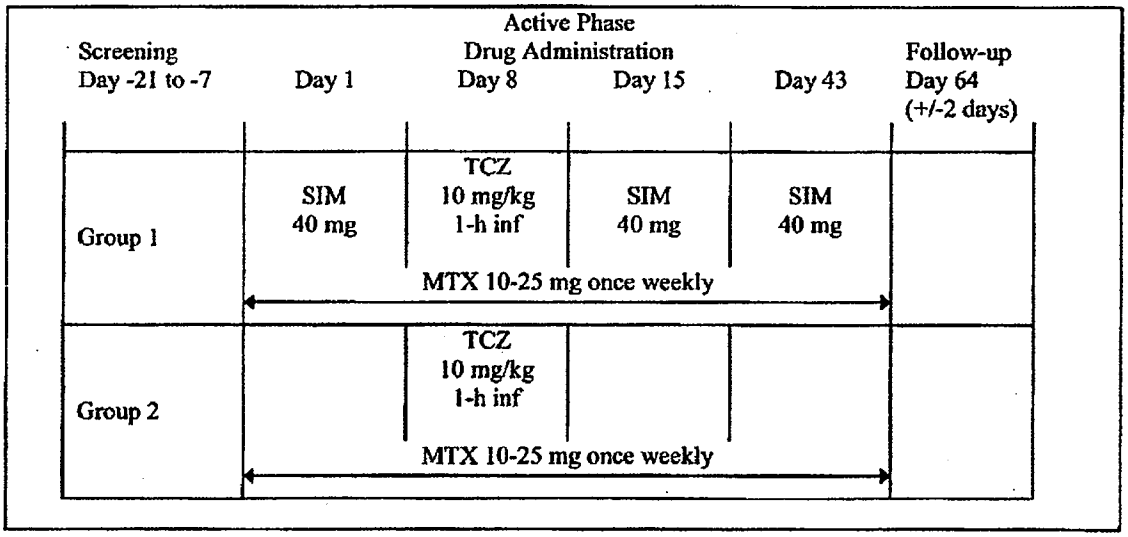
MTX (10-25 mg/week), simvastatin (40 mg), and folic acid (5 mg/week) were administered according to the approved dosing regimen for each medication.

Study Design Elements: It is essential that the population selected for a drug-drug interaction study of this type has the disease and shows evidence of a relatively high degree of IL-6 activity. C-reactive protein is a marker of inflammation that is present at elevated levels in serum of patients with RA. The maximal effect of tocilizumab (TCZ) in normalizing CRP concentrations occurs approximately one week after an intravenous infusion. Such a time-span has also been observed for the induction of cytochrome P450 isoforms and tyrosine aminotransferase. It is

acceptable to examine the possible effects of TCZ on the down-regulation of CYP3A4 in one week after dosing in RA patients.

Study Design: This was a multi-center, open-label, randomized, drug interaction study. A total of 24 RA patients, aged 18 to 75 years, inclusive, were to be enrolled. Twelve patients were to receive TCZ (10 mg/kg), MTX (between 10-25 mg), simvastatin (40 mg), and folic acid (at least 5 mg per week), and 12 patients were to receive TCZ (10 mg/kg), MTX (10-25 mg), and folic acid (at least 5 mg per week). Enrollment was stratified by MTX dose such that approximately equal numbers of patients in three dose ranges were included in the two arms of the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Male/female patients (18-75 years) with RA ≥ 6 months • C-reactive protein (CRP) concentration > 1.5 mg/dL • MTX administered ≥ 12 wks immediately prior to Day 1: stable dose between 10 and 25 mg/wk during last 8 of 12 weeks • If on NSAIDs, stable regimen 4 wks prior to Day 1 • If on oral corticosteroids, dose ≤ 10 mg prednisone or equivalent and stable for 2 wks prior to Day 1 • Willing to provide written ICF • Willing to receive folic acid



Dose and Method of Administration:

- Simvastatin 40 mg (tablet), administered orally as single doses under fasting conditions on days 1, 15, and 43 (Group 1 only)
- MTX 10-25 mg/week (patients' own regimen) administered weekly under fasting conditions throughout the study (Groups 1 and 2)
- Folic acid at least 5 mg/week (patients' own regimen) throughout the study (either as divided daily doses or a single weekly dose)
- Tocilizumab 10 mg/kg administered as single infusion on day 8 (Groups 1 and 2)

Investigational Products:
Tocilizumab (batch Nos: MR5L01, MR4K02, MR4C05, MR6C01, and MR5C06).
Simvastatin (batch Nos: 73152 (mfg 72907) and 73150 (mfg 72907)).

Sample Collection: Blood samples were drawn on days 1, 2, 8, 9, 11, 15, 16, 22, 29, 36, 43, 44, and at follow-up/early withdrawal for the analysis of the three drugs and their metabolites (as appropriate) and safety assessments.

Blood samples were drawn before dosing and at 0.5, 1, 2, 3, 4, 8, 12, and 24 hours post-dose on Days 1, 15, and 43 for the analysis of plasma levels of simvastatin and its metabolite (ß-hydroxy-simvastatin acid).

Blood samples were drawn before dosing and at 0.5, 1, 2, 3, 4, 8, 12, and 24 hours post-dose on Days 1, 15, and 43 for the analysis of plasma levels of MTX and its metabolite (7-hydroxy-MTX).

Blood samples were drawn immediately after the completion of the infusion of TCZ (one hour post-MTX dose) and at 4, 12, and 24 hours after MTX administration on Days 8/9 for the analysis of TCZ serum levels and MTX plasma concentrations. Serum levels of TCZ were also determined from blood samples taken at convenient times on days 11, 22, 29, and 36. In the event of an early withdrawal from the study after TCZ had been administered, an additional blood sample was taken for the measurement of serum levels of TCZ.

Serum levels of CRP, IL-6, sIL-6R, and other biomarkers were measured throughout the study.

Antibodies to TCZ were measured at screening and at follow-up.

Sample Analysis: Serum samples were analyzed for TCZ using a validated specific ELISA method. The calibration range (expressed for the whole serum) was 0.100 to 3.20 µg/mL. The coefficients of variation (CV) of Quality Control samples ranged 6.6-7.7% and the mean accuracy ranged 98.9-102.1%. The analysis was done by [redacted] b(4)

Plasma samples were analyzed for simvastatin and its metabolite, ß-hydroxy-simvastatin acid, using a validated specific liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method (Limit of quantitation [LOQ]: 0.1 ng/mL for simvastatin and ß-hydroxy simvastatin acid). The calibration range was 0.1-30 ng/mL for both analaytes. The inter-assay precision (CV) of Quality Control samples ranged 4.0-6.3% for simvastatin and 1.2-6.9% for simvastatin acid. The accuracy ranged 95.3-104.0% for simvastatin and 97.3-104.2% for simvastatin acid. The analysis was done by . [redacted] b(4)

Plasma samples were analyzed for MTX and its metabolite, 7-hydroxy-MTX, using a validated specific LC-MS/MS method (LOQ: 1 ng/mL for MTX and its metabolite 7-hydroxy-MTX). The calibration range was 1-1000 ng/mL for MTX and 1-150 ng/mL for 7-OH-MTX. The inter-assay precision (CV) of QC samples ranged 4.2-4.6% for MTX and 5.5-7.5% for 7-OH-MTX.

The accuracy ranged 92.1-103.0% for MTX and 94.4-95.3% for 7-OH-MTX. The analysis was done by [redacted] b(4)

Subjects: A total of 23 patients were actually enrolled in the study in four clinical units in the USA: N=12 for Group 1 and N=11 for Group 2. All 23 patients completed the study per protocol and were evaluable for safety, pharmacokinetic, and pharmacodynamic analyses.

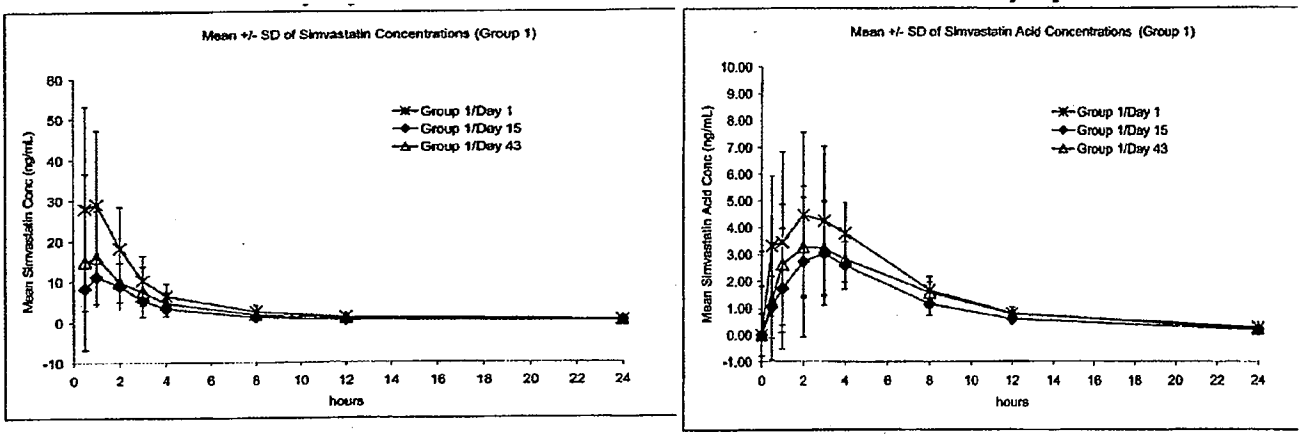
In both groups, there was a higher percentage of female patients (67% for Group 1 and 55% for Group 2), with all patients classified as Caucasians. All but one patient was hepatitis B virus (HBV) and hepatitis C virus (HCV) negative, the positive patient (Group 2) was HBV positive. All 23 patients were folic acid compliant throughout the length of the study. The mean age was similar across the groups at 55 years (Table 1).

Table 1. Characteristics of Groups.

	GROUP 1 N = 12	GROUP 2 N = 11
Sex		
FEMALE	8 (67%)	6 (55%)
MALE	4 (33%)	5 (45%)
n	12	11
Race		
WHITE	12 (100%)	11 (100%)
n	12	11
Age in years		
Mean	55.5	55.7
SD	13.96	13.52
SEM	4.03	4.08
Median	59.0	61.0
Min-Max	28 - 72	28 - 71
n	12	11
Weight in kg		
Mean	87.88	80.48
SD	15.345	16.043
SEM	4.430	4.837
Median	89.55	78.00
Min-Max	63.1 - 111.0	49.1 - 103.4
n	12	11
Height in cm		
Mean	166.4	165.3
SD	11.33	9.07
SEM	3.27	2.73
Median	165.0	166.0
Min-Max	152 - 187	152 - 179
n	12	11

Results:

Effect of TCZ on Simvastatin Pharmacokinetics:
Mean pharmacokinetic profiles of simvastatin and its metabolite, simvastatin acid, following administration of 40 mg of simvastatin either alone (Day 1), or one week (Day 15), or five weeks (Day 43) after TCZ administration are displayed in Figure 1. Corresponding pharmacokinetic parameters are presented in Tables 2 and 3.



Simvastatin Simvastatin Acid

Figure 1. Arithmetic Mean ± SD Plasma Concentration Time Profiles of Simvastatin (Left) and Simvastatin Acid (Right) by Day.

Table 2. Summary of Mean (CV%) Pharmacokinetic Parameters of Simvastatin in Plasma in Treatment Group 1 (n=12).

Parameter	Day 1 MTX + Simv.	Day 15 MTX + Simv.	Day 43 MTX + Simv.
C_{max} (ng/mL)	36.1 (60%)	14.0 (45%)	22.4 (82%)
t_{max} [1] (h)	0.5 (0.5-2)	1.5 (0.5-4)	1.0 (0.5-3)
$t_{1/2}$ (h)	4.39 (41%)	3.95 (43%)	4.14 (29%)
AUC_{last} (h*ng/mL)	102 (43%)	42.9 (41%)	63.2 (54%)
AUC_{inf} (h*ng/mL	105 (44%)	44.9 (41%)	65.2 (52%)
CL/F (L/h)	499 (64%)	1100 (56%)	872 (73%)

Note: Summary of mean values reported as arithmetic means.
Note: (CV%) = coefficient of variation expressed as a percentage: ratio of standard deviation to mean. [1] Median values (min-max) reported for t_{max}.

Table 3. Summary of Arithmetic Mean (CV%) Pharmacokinetic Parameters of Simvastatin Acid in Plasma in Treatment Group 1 (n=12).

Parameter	Day 1 MTX + Simv.	Day 15 MTX + Simv.	Day 43 MTX + Simv.
C_{max} (ng/mL)	5.37 (67%)	3.45 (81%)	3.7 (58%)
t_{max}[1] (h)	2.0 (0.5-4)	2.0 (1-4)	2.0 (0.5-3)
$t_{1/2}$[2] (h)	4.58 (31%)	4.31 (36%)	4.32 (27%)
AUC_{last} (h*ng/mL)	35.1 (72%)	22.4 (75%)	28.0 (63%)
AUC_{inf}[2] (h*ng/mL	37.4 (69%)	24.8 (70%)	34.6 (50%)

Note: Summary of mean values reported as arithmetic means.
Note: (CV%) = coefficient of variation expressed as a percentage: ratio of standard deviation to mean.
[1] Median values (min-max) reported for t_{max}. [2] N=11 on day 15 and N=9 on day 43 (not reported for remaining patients due to inappropriate λ_z).

The plasma concentrations of simvastatin were higher in RA patients on day 1 (where no TCZ had been administered) than those reported in the literature for healthy volunteers. The AUC_{last} and Cmax values of simvastatin in RA patients were 102 ng*h/mL and 36.1 ng/mL, respectively on day 1. In comparison, AUC_{last} of simvastatin following a single oral dose of 40 mg of simvastatin in healthy volunteers ranged from 11 to 25 ng*h/mL and Cmax from 3.2 to 10.5 ng/mL based on references provided in the study report[1,2,3,4]. The AUC of simvastatin was reduced by approximately 58% on day 15 and by approximately 38% on day 43, all compared to day 1.

(Reviewer's Note: Some other references checked by this reviewer suggested that Cmax and AUC of simvastatin in healthy subjects are in similar range as the ones cited by the Sponsor).

Tocilizumab reduced significantly the AUC_{last} and Cmax of simvastatin both on day 15, ie, one week after the injection of TCZ, and on day 43 (ie, five weeks after the infusion of TCZ (Table 2).

Similar findings were observed for simvastatin acid, the main metabolite of simvastatin.

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[1] Najib NM, Idkaidek N, Adel A, *et.al.*, Pharmacokinetics and bioequivalence evaluation of two simvastatin 40 mg tablets (Simvast and Zocor) in healthy human volunteers. **Biopharm Drug Dispos.** 2003;24:183-189.
[2] Neuvonen M, Neuvonen PJ. Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. **Br J Clin Pharmacol.** 2004;58:56-60.
[3] Kyrklund C, Backman JT, Kivistö KT, Neuvonen M, Laitila J, Neuvonen PJ. Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. **Clin Pharmacol Ther.** 2000;68:592-597.
[4] Kantola T, Kivistö KT, Neuvonen PL. Eryhromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. **Clin Pharmacal Ther.** 1998;64:177-182.

The plasma concentrations of simvastatin acid were higher in RA patients on day 1 than those reported in healthy volunteers (e.g. AUC_{last}: 35.1 ng*h/mL in RA patients vs. 18-26 ng*h/mL in healthy volunteers[3,4]. The AUC of simvastatin acid was reduced by approximately 40% on day 15 and by approximately 20% on day 43, all compared to day 1.

*(Reviewer's Note: Some other references checked by this reviewer suggested that Cmax and AUC of simvastatin acid in healthy subjects following 40 mg simvastatin dose are 2 ng/mL and 15-16 ng*h/mL, respectively).*

The effects of TCZ on simvastain and simvastain acid mean exposure ratio (AUC_{last} and Cmax) with their corresponding 90% confidence intervals are presented in Table 4.

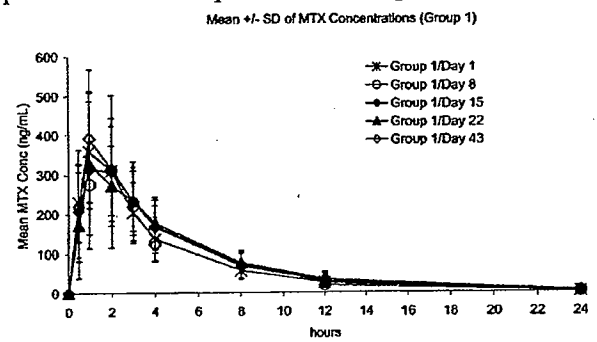
Table 4. Estmated Effect of Tocilzumab on Simvastatin and Simvastain Acid (Group 1).

Estimated Changes in PK

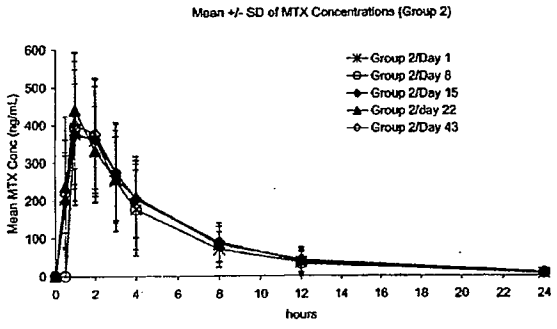
Analyte	Parameter	Comparison	Mean effect ratio (%) Estimate	90% Confidence Region	
SIMVASTATIN	AUClast	Day 15 vs Day 1	43	34	55
		Day 43 vs Day 1	60	46	76
		Day 43 vs Day 15	138	107	177
	CMAX	Day 15 vs Day 1	43	33	55
		Day 43 vs Day 1	61	47	78
		Day 43 vs Day 15	143	111	184
SIMVASTATIN ACID	AUClast	Day 15 vs Day 1	61	49	76
		Day 43 vs Day 1	80	64	100
		Day 43 vs Day 15	131	105	164
	CMAX	Day 15 vs Day 1	59	47	74
		Day 43 vs Day 1	70	56	88
		Day 43 vs Day 15	120	95	150

Effect of TCZ on MTX Pharmacokinetics:

Mean pharmacokinetic profiles of methotrexate following administration of 10-25 mg of MTX on days 1 (alone), 8, 15, 22, and 43 (ie, with and 1, 2, and 5 weeks after TCZ administration) are displayed in Figure 2a and 2b for Group 1 and Group 2, respectively. Corresponding pharmacokinetic parameters are presented in Tables 5 and 6.



a. Group 1



b. Group 2

Figure 3. Arithmetic Mean ± SD Plasma Concentration Time Profiles of Methotrexate by Day.

Table 5. Summary of Arithmetic Mean (CV%) Pharmacokinetic Parameters of Methotrexate in Plasma in Group 1 (n=12).

Parameter	Day 1 MTX + Simv.	Day 8 MTX + TCZ	Day 15 MTX + Simv.	Day 22 MTX alone	Day 43 MTX + Simv.
C_{max} (ng/mL)	383 (29%)	277 (46%)	374 (46%)	363 (41%)	407 (41%)
t_{max} † (h)	1.0 (0.5-2.0)	2.0 (1-4)	1.5 (1-3)	1.0 (0.5-3)	1.0 (1-3)
$t_{1/2}$ (h)	3.36 (23%)	3.21 (32%)	3.58 (27%)	3.44 (29%)	3.38 (25.0)
AUC_{last} (h*ng/mL)	1680 (34%)	1410 (35%)	1860 (42%)	1630 (33%)	1880 (33%)
AUC_{inf} (h*ng/mL	1700 (34%)	1440 (34%)	1890 (41%)	1820 (31%)	1910 (33%)
CL/F (L/h)	10.2 (33%)	12.3 (38%)	9.49 (40%)	9.30 (27%)	9.11 (34%)

† Median values (min-max) reported for t_{max}.
Note: Summary of mean values reported as arithmetic means.
Note: (CV%) = coefficient of variation expressed as a percentage: ratio of standard deviation to mean

Table 6. Summary of Arithmetic Mean (CV%) Pharmacokinetic Parameters of Methotrexate in Plasma in Group 2 (n=11).

Parameter	Day 1 MTX alone.	Day 8 MTX + TCZ	Day 15 MTX alone.	Day 22 MTX alone	Day 43 MTX alone.
C_{max} (ng/mL)	416 (36%)	391 (52%)	416 (37%)	440 (35%)	451 (35%)
t_{max} † (h)	1.0 (1-2)	2.0 (1-2)	2.0 (1-2)	1.0 (1.0-1.1)	1.0 (0.5-2)
$t_{1/2}$ (h)	3.56 (24%)	3.42 (26%)	3.80 (28%)	3.42 (33%)	3.79 (27%)
AUC_{last} (h*ng/mL)	2060 (50%)	2060 (61%)	2250 (46%)	1990 (42%)	2330 (48%)
AUC_{inf} (h*ng/mL	2090 (51%)	2100 (62%)	2300 47%)	2230 (45%)	2380 (49%)
CL/F (L/h)	8.84 (40%)	10.4 (63%)	8.02 (42%)	8.14 (38%)	7.74 (41%)

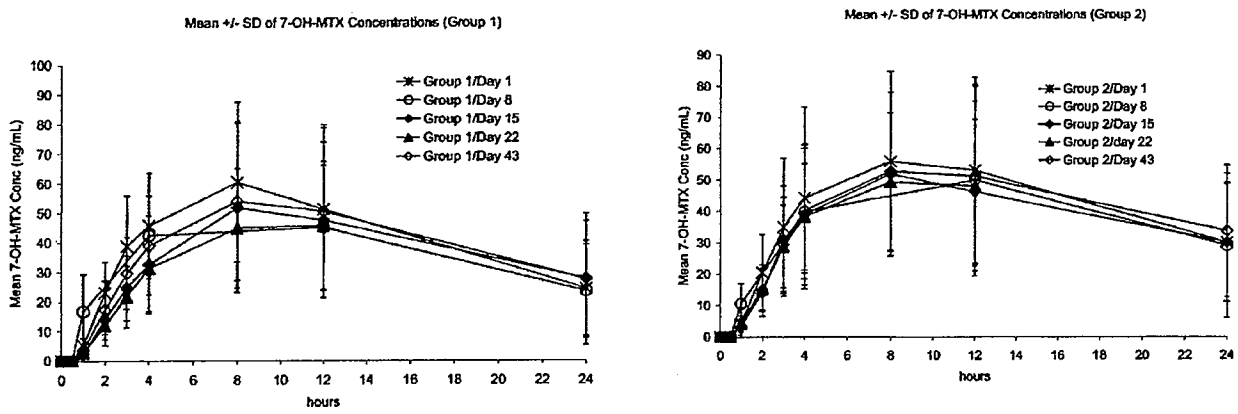
† Median values (min-max) reported for t_{max}.
Note: Summary of mean values reported as arithmetic means.
Note: (CV%) = coefficient of variation expressed as a percentage: ratio of standard deviation to mean.

In both groups, pharmacokinetic profiles of MTX following co-administration with TCZ were not significantly altered. MTX levels appears to be slightly lower in Group 1 (with simvastatin), and the difference may be due to inter-subject variability.

Overall, TCZ did not modify the PK of 7-OH-MTX either (Figure 3, Tables 7 and 8).

The effects of TCZ on MTX and 7-hydroxy-methotrexate mean exposure ratio (AUC_{last}

and Cmax) with their corresponding 90% confidence intervals are presented in Table 9.



a. Group 1 b. Group 2

Figure 3. Arithmetic Mean ± SD Plasma Concentration Time Profiles of 7-OH-MTX by Day.

Table 7. Summary of Arithmetic Mean (CV%) Pharmacokinetic Parameters of 7-OH-Methotrexate in Plasma in Group 1 (n=12).

Parameter	Day 1 MTX + Simv.	Day 8 MTX + TCZ	Day 15 MTX + Simv.	Day 22 MTX alone	Day 43 MTX + Simv.
C_{max} (ng/mL)	61.0 (44%)	48.0 (40%)	53.5 (50%)	47.9 (44%)	55.6 (48%)
t_{max}[1] (h)	8.0 (4-12)	8.0 (4-13)	8.0 (4-12)	8.0 (8-12)	8.0 (4-12)
$t_{1/2}$[2] (h)	8.56 (17%)	not reported N<50%	not reported N<50%	not reported N<50%	9.93 (20%)
AUC_{last} (h*ng/mL)	977 (48%)	845 (44%)	851 (58%)	385 (44%)	933 (55%)
AUC_{inf}[2] (h*ng/mL	918 (54%)	not reported N<50%	not reported N<50%	not reported N<50%	777 (40%)

Note: Summary of mean reported as arithmetic means.

Note: (CV%) = coefficient of variation expressed as a percentage: ratio of standard deviation to mean

[1] Median values (min-max) reported for t_{max}

[2] N=7 on day 1 and 43 (not reported or calculated because of inappropriate λ_z for remaining 5 subjects

Table 8. Summary of Arithmetic Mean (CV%) Pharmacokinetic Parameters of 7-OH-Methotrexate in Plasma in Group 2 (n=11).

Parameter	Day 1 MTX alone.	Day 8 MTX + TCZ	Day 15 MTX alone.	Day 22 MTX alone	Day 43 MTX alone.
C_{max} (ng/mL)	57.8 (52%)	52.5 (59%)	53.3 (49%)	53.2 (48%)	55.9 (51%)
t_{max}[1] (h)	8.0 (4-12)	12.0 (4-12)	8.0 (4-12)	8.0 (8-12)	8.0 4-24)
$t_{1/2}$[2] (h)	not reported N<50%	not reported N<50%	not reported N<50%	not reported N<50%	not reported N<50%
AUC_{last} (h*ng/mL)	1010 (55%)	905 (60%)	904 (50%)	437 (45%)	969 (51%)
AUC_{inf}[2] (h*ng/mL	not reported N<50%	not reported N<50%	not reported N<50%	not reported N<50%	not reported N<50%

Note: Summary of mean reported as arithmetic means.
Note: (CV%) = coefficient of variation expressed as a percentage: ratio of standard deviation to mean.
[1] Median values (min-max) reported for t_{max}
[2] not reported or calculated because of inappropriate λ_z for >50% of subjects

Table 9. Estmated Effect of Tocilzumab on MTX and 7-OH-MTX (Group 2).

Estimated Changes in PK

Analyte	Parameter	Comparison	Mean effect ratio (%) Estimate	90% Confidence Region	
7-OH-METHOTREXATE	AUClast	Day 15 vs Day 1	90	79	103
		Day 43 vs Day 1	97	85	110
		Day 43 vs Day 15	107	94	122
	CMAX	Day 15 vs Day 1	92	82	104
		Day 43 vs Day 1	97	86	110
		Day 43 vs Day 15	106	94	119
METHOTREXATE	AUClast	Day 15 vs Day 1	110	103	118
		Day 43 vs Day 1	114	106	122
		Day 43 vs Day 15	103	97	111
	CMAX	Day 15 vs Day 1	100	92	109
		Day 43 vs Day 1	110	101	119
		Day 43 vs Day 15	110	101	119

PK of TCZ:
The pharmacokinetic parameters of tocilizumab following infusion of 10 mg/kg over an hour in RA patients were in the same range as previously reported in study BP 19461. These parameters were similar in both Groups 1 and 2, indicating that single administration of simvastatin on days 8 and 43 had little effect on tocilizumab pharmacokinetics.

Table 10. Summary of Mean (CV%) Pharmacokinetic Parameters of Tocilzumab.

Parameter	Group 1 (With Simvastatin)	Group 2 (Without Simvastatin)
C_{max} (ug/mL)	253 (26%)	232 (15%)
t_{max}[1] (h)	2.0[2] (1-4)	2.0 (1-12)
$t_{1/2}$ (h)	137 (38%)	151 (39%)
AUC_{last} (h*ug/mL)	40500 (29%)	36900 (26%)
AUC_{inf} (h*ug/mL	41600 (30%)	38200 (29%)
CL/F (mL/h)	0.258 (27%)	0.287 (36%)

Note: Summary of mean reported as arithmetic means.
Note: (CV%) = coefficient of variation expressed as a percentage: ratio of standard deviation to mean.
[1]Median values (min-max) reported for t_{max}.
[2] data for #8619 excluded: apparent mismatch of samples resulting in a t_{max} of 166 h.

IL-6 levels:
The mean (±SEM) serum concentrations of IL-6 over time are displayed in Figure 4 and the mean concentration values (± SD) in Table 11.

In both groups, the mean IL-6 concentrations increased immediately following TCZ administration to peak on day 9, ie, one day after the TCZ administration. Elevated IL-6 levels persisted during 4 weeks, due to the binding of TCZ to IL-6 receptors. They nearly reached baseline values about 8 weeks after TCZ administration. No significant differences were observed between the two groups.

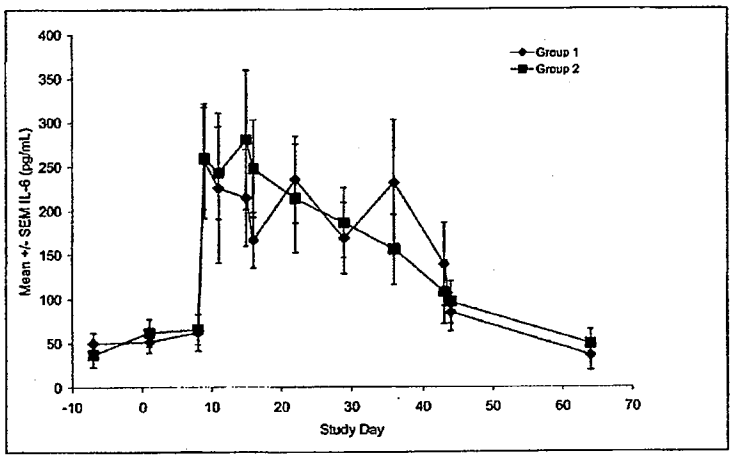


Figure 4. Absolute Serum IL-6 Concentrations (Mean ± SEM) Over Time per Group.
Table 11. Mean (± SD) IL-6 Values Over Time per Group.

IL-6 (pg/mL)													
	Scheduled Day												
Group 1	**Screen**	**1**	**8**	**9**	**11**	**15**	**16**	**22**	**29**	**36**	**43**	**44**	**FU**
n	12	12	11	11	9	11	11	11	10	11	12	12	11
Mean	49.8	51.6	62.3	256	226	215	167	235	169	231	139	84.5	35.2
SD	44.4	43	69.2	225	268	190	109	171	133	238	164	73.7	54.4
Group 2	**Screen**	**1**	**8**	**9**	**11**	**15**	**16**	**22**	**29**	**36**	**43**	**44**	**FU**
n	11	11	11	11	10	11	11	10	11	11	11	11	11
Mean	37.0	62.0	65.5	259	243	281	248	214	186	156	107	96.0	48.4
SD	46.0	52.4	57.6	192	166	262	182	204	131	133	118	79.2	54.1

Anti-TCZ Antibody:
There was one patient (57721/8622) who had positive results in the screening and confirmation assay for anti- TCZ antibodies at screening and at treatment follow-up. For this patient, only below-the-lower-limit-of-quantification (BLQ) values were detected for anti- TCZ Fab, anti-TCZ IgE, and anti- TCZ neutralizing antibodies.

Safety Summary:
Overall, administration of a single dose of TCZ (10 mg/kg) together with methotrexate (10-25 mg) once weekly, and at least 5 mg of folic acid once weekly, with or without single doses of simvastatin (40 mg), were well tolerated. There were no deaths, SAEs or AEs leading to withdrawal in this study. There was no apparent difference in incidence of AEs between the two treatment groups. Gastrointestinal disorders and infections/infestations were the most commonly reported type of AEs. The majority of AEs were mild to moderate in intensity, with one AE (fatigue) in Group 1 and one AE (rheumatoid arthritis) in Group 2 classified as severe.

The main laboratory safety test finding observed in this study following administration of TCZ 10 mg/kg was a decrease in absolute neutrophil count, an effect generally thought to be associated with the blockade of IL-6 receptors, in parallel with an increase of triglycerides. Most other safety laboratory test results remained within normal limits, including liver function tests, other lipid parameters, and immunoglobulins. There were no vital sign or ECG abnormalities of clinical relevance recorded during the study and no treatment emergent anti- TCZ antibodies were detected.

Discussion:
Administration of simvastatin 40 mg alone on day 1 in RA patients resulted in higher plasma concentrations of simvastatin and simvastatin acid than those reported in the literature for healthy subjects without inflammatory disease, corroborating the expectation that RA patients, who exhibit elevated concentrations of IL-6, present higher exposure to CYP3A4 substrates (Tables 12 and 13). Single-dose administration of simvastatin 40 mg one week after the infusion of TCZ 10 mg/kg significantly reduced the exposure to simvastatin and its metabolite by 57% and 39%, respectively. Of note, the simvastatin and simvastatin acid levels in those patients with

RA treated with tocilizumab were close to but still slightly higher than those reported in the literature for healthy subjects without inflammatory disease. When simvastatin 40 mg was administered five weeks after TCZ infusion, the exposure to the drug and its metabolite was still reduced compared to day 1, but to a lesser extent: AVC decreased by 40% for simvastatin and by 20% for simvastatin acid (Tables 12 and 13).

Simvastatin was not administered on Day 8, so it is not possible to know whether there may be "acute" effect on simvastatin from coadministration with TCZ.

Table 12. Comparison of exposure of simvastatin obtained from this study vs. historical data in healthy subjects (40 mg simvastatin).

	Exposure in Healthy Subject (various literature sources)	Exposure in RA patients (this Study) before TCZ infusion	Exposure in RA patients (this Study) 7-days after single dose TCZ infusion	Exposure in RA patients (this Study) 35-days after single dose TCZ infusion
Mean AUC (hr•ng/mL)	11-25	105	45	65
Mean Cmax (ng/mL)	3.2-10.5	36	14	22.4

Table 13. Comparison of exposure of simvastatin acid obtained from this study vs. historical data in healthy subjects (40 mg simvastatin).

	Exposure in Healthy Subject (various literature sources)	Exposure in RA patients (this Study) before TCZ infusion	Exposure in RA patients (this Study) 7-days after single dose TCZ infusion	Exposure in RA patients (this Study) 35-days after single dose TCZ infusion
Mean AUC (hr•ng/mL)	15-26	35.1	22.4	28
Mean Cmax (ng/mL)	2	5.4	3.5	3.7

Small increases of methotrexate exposure were observed one week (+10%) and five weeks (+ 14%) post TCZ administration. This was associated with corresponding minor decreases of exposure to its metabolite, 7-hydroxy-methotrexate, of 10% and 3%, respectively. Overall, intravenous infusion of TCZ 10 mg/kg had no relevant effect on methotrexate pharmacokinetics.

The data is consistent with the fact that P450s are not the major enzymes for MTX metabolism. And the effect of TCZ is on P450 regulation.

The comparison of the pharmacokinetic profiles of methotrexate and TCZ between patients who did (Group 1) and did not (Group 2) receive single doses of simvastatin suggested that simvastatin had little effect on the pharmacokinetics of methotrexate and TCZ.

Conclusion:

In conclusion, similar to another drug interaction study conducted by the Sponsor (Study 220JP), this study provided *in vivo* evidence that TCZ could modulate P450 3A4 enzyme levels by binding to IL-6 receptor. The exposure levels of simvastatin (a CYP3A4 substrate) can be altered following TCZ administration (similar to induction effect). The administration of tocilizumab in rheumatoid arthritis patients significantly reduced the exposure to simvastatin to levels slightly higher than those found in non-RA patients. The effect persisted for five weeks after tocilizumab administration. In addition, tocilizumab had no relevant effect on methotrexate exposure.

As this study only studied a single dose of TCZ, the results may not fully mimic the clinical situation where TCZ will be administered every 4 weeks and IL-6 levels may be different along the timecourse. The P450 expression levels would determine the *in vivo* exposure for a drug that is a P450 substrate.

Drug interactions mediated by TCZ would have clinical implication for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted based on response measurements (e.g., warfarin) or drug monitoring (e.g., cyclosporine or theophylline) where a decrease of up to 50% could become clinically relevant. Upon initiation of TCZ in RA patients, depending on the P4503A4 level change, decrease in statin exposure is expected and may lead to decrease in lipid lowering efficacy. Conversely, because of the lower P4503A4 expression in RA patients, the initiation dose of statin should be low to avoid high exposure that may lead to unwanted side effects such as rhabdomyolysis. Upon withdrawal of TCZ in RA patients, caution should also be exercised as levels for drugs that are CYP substrates will increase.

Linked Applications	Sponsor Name	Drug Name
IND 11972	HOFFMANN-LA ROCHE INC	Humanized Monoclonal Antibody (MRA) to Interleukin-6 Receptor

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/s/

LEI ZHANG
08/11/2008

SURESH DODDAPANENI
08/11/2008

CLINICAL PHARMACOLOGY REVIEW

BLA	STN 125276
Submission Dates:	11/19/2007; 6/30/2008; 7/8/2008
Brand Name	ACTEMRA®
Generic Name	Tocilizumab (RO4877533 or myeloma receptor antibody), recombinant humanized anti-human monoclonal antibody
OCP Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram, Ph.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Sponsor	Roche Pharmaceuticals
Relevant IND	BB-IND 11,972
Submission Type; Code	NME; 1S
Formulation; Strength(s); Administration Route	Concentrate solution; 20 mg/mL; Intravenous infusion
Proposed Indication	Indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who are naïve to treatment with, or who had an inadequate response to, one or more DMARDs or TNF antagonists. ACTEMRA can be used alone or in combination with methotrexate or other DMARDs
Proposed Dosage Regimen	The recommended dose of ACTEMRA for adult patients with rheumatoid arthritis is 8 mg/kg given once every 4 weeks as a 60-minute single intravenous drip infusion

Table of Contents

1 Executive Summary

1.1 Recommendation

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

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Tocilizumab (RO4877533, TCZ), also referred to as myeloma receptor antibody (MRA), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G_1 (IgG_1) subclass directed against the soluble and membrane-bound interleukin 6 receptor (IL-6R). TCZ has a molecular weight of approximately 149 kDa, of which ⌜ ⌟ b(4)
TCZ is produced using a ⌜ ⌟

This is the first BLA application for tocilizumab in the U.S. (IND 11,972). The Sponsor is seeking the indication for the treatment of adult rheumatoid arthritis (RA). Tocilizumab is marketed in Japan since 2006 for the indication of Castleman's disease. In April 2008, it was approved in Japan for the indication of adult RA and juvenile RA (JRA).

Rheumatoid arthritis (RA) is the most common of the incurable and potentially disabling chronic systemic inflammatory autoimmune diseases affecting approximately 0.5-1% of the population worldwide. The disease, which is 2.5-fold more prevalent in women than in men is characterized by symmetric synovitis and erosive arthritis, often rapidly progressive with joint damage apparent soon after the onset of symptoms. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of RA. Thus, the inhibition of the biological activity of IL-6 and/or its receptor may represent a promising new approach for the treatment of RA. The Sponsor developed TCZ as a novel therapeutic molecule with new mechanism of action for RA via IL-6R blocking. An AC meeting will be held on July 29, 2008 to discuss this application.

The clinical development program included five pivotal Phase 3 studies. The doses of 4 mg/kg and 8 mg/kg given every 4 weeks for 24 weeks were studied in the trials. The Sponsor proposed a dose regimen of 8 mg/kg every 4 weeks.

Mechanism of Action: Interleukin (IL)-6 is a pleiotropic cytokine that has important roles in the regulation of the immune response, inflammation, and hematopoiesis. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of rheumatoid arthritis (RA). Tocilizumab selectively binds to soluble and membrane-bound human IL-6 receptors, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6, and may provide an alternative mechanism for the treatment of RA.

Product Development and Comparability among Product Lots: During the development program of tocilizumab, changes have been made to the manufacturing processes of both drug substance and drug product. These are referred to as 1st generation (G1) to 4th generation (G4) processes for drug substance and DP1, DP2 and DP3 for drug product generations.

G1 and G4 are most relevant to the TCZ application in the U.S. Drug supply derived from the G4 process was used by Roche in Phase 1 (BP19461) and Phase 3 studies worldwide and is intended for marketing. DP2 (with G4 drug substance) has been used in the pivotal Phase 3 studies. Tocilizumab derived from the G4 and DP3 generations, which has been used in the ongoing Phase 3 study (WA17823) and the long-term extension studies, is intended for commercial supply.

Comparability of the different generations of drug substance and drug product was established using analytical methods and bioassays. No nonclinical or clinical pharmacokinetic (PK) studies were performed to assess the comparability of tocilizumab.

The comparability results from the analytical testing and bioassays are reviewed by the product reviewer, Dr. Feldman. The assessment confirmed that comparability between all generations of drug substance and drug product was established. Refer to Product review for details.

Pharmacokinetics Findings:

Healthy Subjects: Human PK studies showed that clearance (CL) of tocilizumab was concentration-dependent. CL decreased with increased dose. Mean CL was estimated as 0.609 mL/h/kg for the 2 mg/kg dose and decreased with increasing doses to 0.192 mL/h/kg for the highest dose of 28 mg/kg. At the 10 mg/kg single dose in healthy subjects, mean CL was 0.24 mL/hr/kg and mean apparent $T_{1/2}$ was 201 hours (8 days).

RA Patients: The PK of tocilizumab were similar in healthy subjects (HV) and RA patients based on the comparison of non-compartmental PK data from Study BP19461 in HV, Study LRO300 in RA patients, and mean estimates from the POP-PK analysis in RA patients. At the 10 mg/kg single dose in RA patients, mean CL was 0.26 mL/hr/kg and mean apparent $T_{1/2}$ was 158 hours (7 days).

Population PK Analyses: POP-PK analysis was conducted based on data obtained from 4 Phase 3 studies. Concentration-dependent CL was described by the PK model where total CL is the sum of both linear (concentration-independent) and non-linear (concentration-dependent) CL. Mean linear CL was 0.18 mL/h/kg (12.5 mL/h). The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. Therefore, the average contribution of the nonlinear (concentration-dependent) CL to the total CL was less at 8 mg/kg than at 4 mg/kg tocilizumab every 4 weeks.

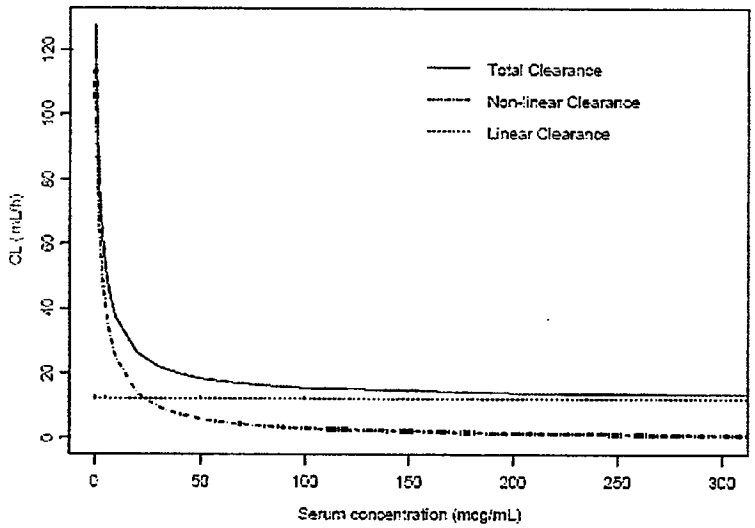


Figure 1. Relationship between Total Clearance, Nonlinear Clearance and Linear Clearance and Tocilizumab Serum Concentrations (Based on Final PopPK Estimates).

PK parameters estimated from the model are listed in Table 1.

Table 1. Summary of Mean (± SD) Predicted AUCτ, Cmax and Cmin for the First Dosing Interval and at Steady-State following 4 and 8 mg/kg Tocilizumab every 4 Weeks.

Pharmacokinetic Parameter	4 mg/kg every 4 weeks			8 mg/kg every 4 weeks		
	First Dosing Interval	Steady-State	R_{AC}	First Dosing Interval	Steady-State	R_{AC}
AUC_τ (h·µg/mL)	11800 ± 5000	13000 ± 5800	1.11	28800 ± 11600	35000 ± 15500	1.22
C_{max} (µg/mL)	86.8 ± 40.9	88.3 ± 41.4	1.02	174 ± 81.9	183 ± 85.6	1.06
C_{min} (µg/mL)	0.76 ± 0.91	1.49 ± 2.13	1.96	4.14 ± 4.29	9.74 ± 10.5	2.35

R_{AC}: accumulation ratio; a simulation experiment was performed with 48 weeks of treatment and the two doses tested in Phase III (4 and 8 mg/kg every 4 weeks) with 10 studies (replicates) (n = 1793 patients per replicate); AUC_τ: AUC within dosing interval

The $T_{1/2}$ of tocilizumab is concentration-dependent. The apparent $T_{1/2}$ ranged from 10 to 19 days for 8 mg/kg every 4 weeks at steady-state corresponding to C_{min} and C_{max}, respectively.

Pharmacokinetics in Special Populations: Although no specific studies were conducted, based on the results of the POP-PK analyses, age, gender, race and ethnicity had no impact on the PK of tocilizumab in adult RA patients.

The Sponsor requested a deferral for studying safety and efficacy in pediatric patients.

No formal PK studies were conducted in subjects with renal or hepatic impairment.

The Sponsor conducted an exploratory study (MRA221JP) in patients with mild, moderate and severe renal impairment, and no difference in PK was observed between RA patients with and without renal impairment (characterized by CLcr).

Pharmacodynamic Findings: IL-6, sIL-6R, and C-reactive protein (CRP) were monitored in multiple studies as PD indicators. IL-6 and sIL-6R are directly linked to the mechanism of action of tocilizumab. CRP is synthesized by hepatocytes as a direct effect of IL-6 signaling in response to proinflammatory cytokines. CRP is used in the diagnosis of RA and is also included in the disease activity core set DAS28.

Following administration of tocilizumab, IL-6 levels initially increased and then generally decreased with time. High and sustained sIL-6R levels were observed with only a slight fluctuation within the dosing interval following administration of TCZ at 8 mg/kg every 4 weeks. CRP levels were markedly suppressed as early as week 2 and sustained around the normal range during the dosing interval with little fluctuation at a TCZ dose of 8 mg/kg every 4 weeks. A larger fluctuation in CRP levels was observed at a dose of 4 mg/kg every 4 weeks.

Exposure-Response:
Dose Selection: Two Phase 2 studies were conducted that studied doses of 2, 4, and 8 mg/kg every 4 weeks in RA patients with and without MTX. Based on the outcome, 4 and 8 mg/kg were selected for studying in Phase 3 studies.

ER for Efficacy: Both 4 and 8 mg/kg every 4 week doses showed statistically significant ACR20 response compared to placebo at Week 24. A higher proportion of patients achieved ACR20 under 8 mg/kg dose than 4 mg/kg dose.

ER for Safety: Although there is no clear relationship of safety with regard to dose or exposure, the 4 mg/kg dose of tocilizumab appeared to be associated with a lower incidence of serious infection than the 8 mg/kg dose when used in combination with a DMARD; no GI perforation events were reported in patients on 4 mg/kg while 3 GI perforations occurred in patients on TCZ 8 mg/kg.

Immunogenicity: A very small proportion of patients tested positive for anti-TCZ antibodies (46/2553, 1.8%) in the TCZ treatment groups of the 6-month safety population (all studies). Approximately 6% (10/159) of patients tested for events of potentially immunogenic origin were positive for anti-TCZ antibodies. In 4 pivotal Phase 3 studies (Studies 17822, 17824, 18062 and 18063), a total of 24 out of 1747 (1.4%) patients developed anti-TCZ antibodies. Of the 24 patients who developed anti-TCZ antibodies, 9 patients developed antibodies of the Ig class, predominantly IgG or IgM, 18 patients developed neutralizing anti-TCZ antibodies, and 4 patients developed uncharacterized positive antibodies (screen/confirmation positive). Patients could appear in multiple categories. It seems that the TCZ 8 mg/kg + MTX/DMARD group had a higher incidence of anti-TCZ antibodies and neutralizing antibody development.

The limited cases indicated that anti-TCZ antibodies or neutralizing antibodies had no apparent impact on the PK, safety or efficacy of TCZ.

Drug-Drug Interactions: IgG antibodies are not metabolized by P450s. Therefore, direct pharmacokinetic interaction via the CYP pathway is not expected between tocilizumab and co-administered small molecular weight drugs. POP-PK analysis showed that commonly co-administered drugs in RA patients including methrotrexate, leflunomide, NSAIDs (e.g., naproxen, ibuprofen, celecorxib, diclofenac, meloxicam) and analgesics (e.g., acetaminophen, codeine, tramadol) had no effect on tocilizumab PK. Tocilizumab, however, might indirectly influence the expression level of CYP enzymes leading to altered P450 activities in RA patients because IL-6 is known to reduce the expression level of multiple CYP enzymes including CYP3A4. Therefore, drug interaction with P450 substrate drugs caused by the modulation of P450s was anticipated.

In vitro data with human hepatocytes showed that co-incubation with tocilizumab inhibited the IL-6-mediated down-regulation of CYP450 enzymes including CYP1A2, 2B6, 2D6, 2C9, 2C19, and 3A4. CYP2E1 was least affected. Study 220JP was an *in vivo* drug interaction study with dextromethorphan (CYP2D6 and CYP3A4) and omeprazole (CYP2C19). The study results showed that co-administration of tocilizumab 8 mg/kg resulted in a decrease in exposure of omeprazole (~50%) in CYP2C19 extensive metabolizers indicating reverse of down-regulation of CYP2C19. Although TCZ showed a little effect on the exposure of dextromethorphan, the exposure of dextrorphan (a CYP2D6 metabolite from dextromethorphan) level decreased. Dextrorphan undergoes further metabolism by CYP3A4.

The Sponsor is conducting a new drug interaction study (Study WP18663) with simvastatin as the CYP3A4 substrate.

It is not clear about the P450 enzyme expression levels in RA patients (who have elevated IL-6) with TCZ compared to those in healthy subjects who have normal IL-6 levels. The P450 expression levels would determine the *in vivo* exposure for a drug that is a P450 substrate.

Drug interactions may have clinical implication for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted based on response measurements (e.g., warfarin) or drug monitoring (e.g., cyclosporine or theophylline) where a decrease of up to 50% could become clinically relevant. In addition, depending on the P4503A4 level change, decrease in oral contraceptive (CYP3A4) exposure is expected and may lead to decrease in efficacy.

Tocilizumab has not been studied in combination with biological DMARDs such as TNF antagonists.

QT/QTc Evaluation: Although it is not generally required for a biological product, the Sponsor conducted a thorough QT/QTc study for TCZ (Study 19461, Part 2). The Sponsor conducted this study to provide data to address the precautionary statement in the label approved for TCZ in Japan for the orphan indication of Castleman's disease: "In the clinical studies, cardiac abnormalities were observed and therefore, electrocardiography should be conducted periodically with a caution for the changes during the treatment with ACTEMRA". The study is on-going at the time of BLA submission.

Adverse Events: The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions (occurring in ≥ 5% of patients treated with ACTEMRA monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT. Decreases in neutrophil counts and elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed in patients receiving ACTEMRA. Deaths were uncommon, but were observed in all treatment arms during the 6-month controlled period, except in the TCZ 4 mg/kg treatment arm. The highest proportion of deaths (3/288, 1%) occurred in the TCZ 8 mg/kg monotherapy arm of Study WA17824.

An Optional Inter-Divisional-Level Clinical Pharmacology briefing took place on July 17, 2008.

Lei Zhang 7/28/08

Lei Zhang, Ph.D.

B.V.Atul 07/28/08

Venkatesh Atul Bhattaram, Ph.D.

Concurrence: 7/28/08

Jogarao Gobburu, Ph.D.

07/28/08

Suresh Doddapaneni, Ph.D

2 Question-Based Review (QBR)

Reviewer's Notes: Tocilizumab (TCZ), RO4877533, and MRA are used interchangeably in this review. The proposed trade name is ACTEMRA®.

2.1 General Attributes

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

Chemistry and Physico-Chemical Properties: Tocilizumab (RO4877533) is a humanized anti-human IL-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass produced using recombinant DNA technology.

The tocilizumab molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulfide linkages. The Molecular formula for TCZ is $C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$ (polypeptide moiety only).

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

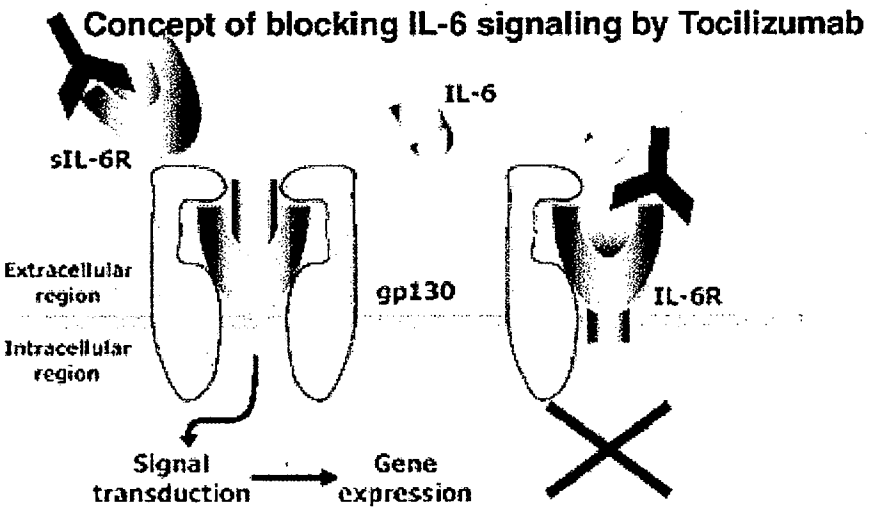
Tocilizumab (TCZ) was produced by selecting a mouse anti-human IL-6R monoclonal antibody with the most potent inhibitory activity in an *in vivo* nude mouse myeloma cell xenograft system. Humanization was achieved by grafting the complementarity determining regions (CDR) of the mouse anti-human IL-6R monoclonal antibody onto a human $IgG_1\kappa$ antibody framework (H_2L_2 structure), followed by transfection of both light and heavy chain genes into Chinese hamster ovary (CHO) cells to produce a humanized antibody.

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

2.1.2 What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?

Mechanism of Action: IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis. IL-6 has been implicated in the pathogenesis of diseases including other inflammatory diseases, osteoporosis and neoplasia.

Tocilizumab selectively binds to soluble and membrane-bound human IL-6R, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6 (Figure 2.1.2.1). The data obtained from *in vitro* assays demonstrate that tocilizumab has essentially no or minimal complement dependent cytotoxicity (CDC) activity, and little or no significant antibody dependent cellular cytotoxicity (ADCC) activity.



Blockade of IL-6 signals by anti-IL-6 receptor antibody (MRA, Tocilizumab).
h, human; IL, interleukin; sIL-6R, soluble interleukin-6 receptor.

Figure 2.1.2.1.

Proposed Indication. Indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who are naïve to treatment with, or who had an inadequate response to, one or more DMARDs or TNF antagonists.

ACTEMRA can be used alone or in combination with methotrexate or other DMARDs.

Proposed Dosage and Route of Administration. The recommended dose of ACTEMRA for adult patients with rheumatoid arthritis is 8 mg/kg given once every 4 weeks as a 60-minute single intravenous drip infusion.

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical studies that have been conducted during the development of tocilizumab and have contributed PK and PD data are summarized as follows (Table 2.2.1.1):

- 3 SAD studies (2 in HV and 1 in RA patients)
- 3 multiple dose Phase 2 studies in RA patients
- 3 additional single dose studies (1 in HV and 2 in RA patients)
- 4 multiple dose pivotal Phase 3 studies in RA patients

In addition, 2 clinical pharmacology studies are on-going: one is for drug interaction with MTX and simuvastatin (Study WP18663) and the other is thorough QT (Study BP19461 Part 2).

Table 2.2.1.1. Overview of Studies with Pharmacokinetic and Pharmacodynamic Data.

	Protocol Number	Study Objective	Study Design	Tocilizumab Dose	Dosing Regimen	Study Population (Location)	No. of Subjects Planned	No. of Subjects Dosed
Single Dose	BP19461 (part 1)	ST, PK	Double blind, randomized, placebo controlled, single center	2, 10, 20, 28 mg/kg	SAD, IV	HV (UK)	38-62	36
	MRA001JP*	ST, PK, MTD determination	Single blind, randomized, placebo controlled, single center	0.15, 0.5, 1, 2 mg/kg	SAD, IV	HV (Japan)	42	28
	LRO300	ST, PK, efficacy, antigenicity	Double blind, randomized, placebo controlled, multicenter	0.1, 1, 5, 10 mg/kg	SAD, IV	RA (UK)	48	45
Multiple Dose	MRA002JP	ST, PK, efficacy	Open-label, non-randomized, multicenter	2, 4, 8 mg/kg	MAD, every 2 weeks up to 24 weeks treatment, IV	RA (Japan)	15	15
	MRA009JP	ST, PK, efficacy	Double-blind, placebo controlled, randomized, parallel group, multicenter	4, 8 mg/kg	MD, once every 4 weeks for 12 weeks, IV	RA (Japan)	132	163
	LRO301	ST, PK, efficacy	Double-blind, placebo controlled, randomized, parallel group, multicenter.	2, 4, or 8 mg/kg	MD, once every 4 weeks, IV	RA (Europe, 14 countries)	300-350	359
Ongoing	BP19461 (part 2)	ST, PK, ECG	Double blind, randomized, placebo controlled, active comparator, parallel, multicenter	10, 20 mg/kg	SD, IV	HV (UK, New Zealand)	120	ongoing
	WP18663	PK, DDI	Open label, randomized, multicenter	10 mg/kg	SD, IV	RA (US)	24	ongoing
Additional Studies	MRA220JP	ST, PK, efficacy, DDI	Open label, non-randomized, single center	8 mg/kg	SD, IV	RA (Japan)	31	31
	MRA221JP	ST, PK, efficacy, renal impairment	Open label, non-randomized, multicenter	8 mg/kg	SD, IV	RA, Renal impaired (Japan)	10	14
	MRA004JP	ST, PK, ECG	Open label, non-randomized, single center	2 mg/kg	SD, IV	HV (Japan)	6	6

DDI, drug-drug interaction study; DMARD, disease-modifying antirheumatic drug; ECG, assessment of potential electrocardiogram changes; HV, healthy volunteers; IV, intravenous; MAD, multiple ascending dose; MD, multiple dose; MTD, maximum tolerated dose; MTX, methotrexate; PD, pharmacodynamics; PK, pharmacokinetics; po, oral; pop population; RA, rheumatoid arthritis patients; ST, safety and tolerability; SAD, single ascending dose; SD, single dose; TNF, tumor necrosis factor;
*The Sponsor prematurely terminated this study due to safety concerns related to inclusion of healthy volunteers (see Section 2.1.1.2); ** safety population

	Protocol Number	Study Objective	Study Design	Tocilizumab Dose	Dosing Regimen	Study Population (Location)	No. of Subjects Planned	No. of Subjects Dosed**
Phase III	WA17822	Efficacy, safety, popPK	Double blind, randomized, placebo controlled,	4 or 8 mg/kg	MD, once every 4 weeks for 24 weeks, IV; MTX 10-25 mg/week po	RA in MTX inadequate responders (Worldwide, 17 countries)	630	622
	WA18063	Efficacy, safety, popPK	Double blind, randomized, placebo controlled,	8 mg/kg	MD, once every 4 weeks for 24 weeks, IV; Standard DMARD(s)	RA in inadequate responders to DMARDs (Worldwide, 18 countries)	1200	1216
	WA18062	Efficacy, safety, popPK	Double blind, randomized, placebo controlled	4 or 8 mg/kg	MD, once every 4 weeks for 24 weeks, IV; MTX 10-25 mg/week po	RA in inadequate responders to anti-TNF agent(s) (Worldwide, 13 countries)	450	498
	WA17824	Efficacy, safety, popPK	Double blind, double dummy, randomized, placebo controlled	8 mg/kg	MD, once every 4 weeks for 24 weeks, IV; or MTX 7.5-20 mg/week po	RA; MTX naïve or MTX discontinued but not due to lack of efficacy of toxic effect (Worldwide, 18 countries)	650	673

DDI, drug-drug interaction study; DMARD, disease-modifying antirheumatic drug; ECG, assessment of potential electrocardiogram changes; HV, healthy volunteers; IV, intravenous; MAD, multiple ascending dose; MD, multiple dose; MTD, maximum tolerated dose; MTX, methotrexate; PD, pharmacodynamics; PK, pharmacokinetics; po, oral; pop, population; RA, rheumatoid arthritis patients; ST, safety and tolerability; SAD, single ascending dose; SD, single dose; TNF, tumor necrosis factor;
*The Sponsor prematurely terminated this study due to safety concerns related to inclusion of healthy volunteers (see Section 2.1.1.2); ** safety population

The clinical database comprises of five Phase 3 studies (Table 2.2.1.2). A total of 3,192 patients provide a total of 2,755 patient-years of exposure at the TCZ 8 mg/kg dose and 923 patients provide a total of 341 patient-years of exposure at the TCZ 4 mg/kg dose. In the 24-week core studies, 1,454 patients received control treatment, with a total of 585 patient-years of exposure. A total of 2570 patients received treatment with the TCZ 8 mg/kg dose for at least 6 months, 1443 patients were treated for 12 months and 554 patients were treated for at least 18 months. The data were used to support the use of TCZ 8 mg/kg alone or in combination with methotrexate (MTX) or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of adults with moderate to severe, active RA.

Table 2.2.1.2. Key Design Features of the 5 Pivotal Phase 3 Studies.

	WA17822	WA17823	WA17824	WA18062	WA18063
Design and Duration	DB, R, PC: 24-week	DB, R, PC: year 1 DB, year 2 OL	DB, DD, R, PC: 24-week	DB, R, PC: 24-week	DB, R, PC: 24-week
Patient Population	Moderate to severe active RA in MTX inadequate responders	Moderate to severe active RA in MTX inadequate responders	Active RA; MTX naïve or MTX discontinued but not due to lack of efficacy or toxic effect	Moderate to severe active RA in patients with inadequate response to anti-TNF agent(s)	Moderate to severe active RA in patients with inadequate response to DMARDs
Treatment	**3 arm study:** Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	**3 arm study:** Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	**2 arm study:** Tocilizumab: 8 mg/kg iv every 4 weeks **or** MTX 7.5-20 mg/week (po) **Substudy includes 3rd arm:** Placebo (8 weeks placebo then 16 weeks TCZ 8 mg/kg)	**3 arms:** Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks plus MTX 10-25 mg/week	**2 arms:** Tocilizumab: 8 mg/kg or placebo iv every 4 weeks plus standard DMARD(s)
Escape therapy	Week 16: TCZ 8 mg/kg	Week 16 onwards: TCZ 4 or 8 mg/kg	Substudy only, up to Week 8: TCZ 8 mg/kg	Week 16: TCZ 8 mg/kg	Week 16: adjustment of background DMARD
Total Randomized Patients	623	1196	673	499	1220
Primary Endpoint at Week 24	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate

DB = double blind, R = randomized, PC = placebo controlled, DD = double dummy

In addition there are 2 Long-Term Extension Studies:

Patients who completed the 6-month pivotal studies (WA17822, WA18063, WA18062 and WA17824) were allowed to transition into one of two open-label, long-term extension studies (a brief summary is provided below).

• **Study WA18695** is an open-label extension study to assess the long-term safety of TCZ 8 mg/kg + MTX in patients completing treatment in WA17822.

• **Study WA18696** is an open-label extension study to assess the long term safety of TCZ 8 mg/kg as monotherapy or in combination with background DMARD therapy in patients completing treatment in WA17824, WA18062, WA18063 and WP18663.

2.2.2 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of safety and efficacy?

Efficacy:
Primary: ACR20 (American College of Rheumatology) response at Week 24
Secondary: ACR50/70 response at Week 24

A positive ACR20 response requires at least a 20% improvement compared to baseline in both tender and swollen joint counts, as well as in 3 out of 5 of the additional ACR core set variables: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI) and an acute phase reactant (C-Reactive Protein (CRP)) or Erythrocyte Sedimentation rate (ESR) (Table 2.2.2.1). CRP was used as the acute phase reactant for the calculation of the ACR response since this was analyzed centrally and therefore would be expected to be more reproducible than ESR which was analyzed locally. However, where the percentage change from baseline for CRP was missing, ESR will be substituted.

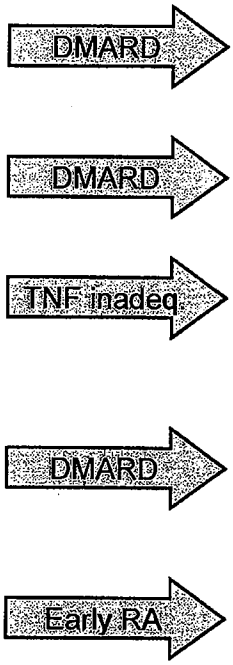
Table 2.2.2.1. Core Parameters Assessed for ACR and EULAR Indices of Disease Activity.

Parameter	ACR	EULAR (DAS28)
SJC/TJC	Yes SJC 66 joints TJC 68 joints	Yes SJC 28 joints TJC 28 joints
Patient's global assessment of disease activity (GH)	Yes	Yes
Physician's global assessment of disease activity	Yes	No
Patient's assessment of pain	Yes	No
Acute Phase Reactants	CRP or ESR[a]	ESR
Health Assessment Questionnaire (HAQ)	Yes	No

[a] CRP was used for the calculation of ACR response; where the percentage change from baseline in CRP was missing, ESR was substituted

All 5 pivotal studies support the conclusion that tocilizumab is effective (Table 2.2.2.2). Subgroup analyses and secondary endpoints are consistent with the primary analysis. Refer to Dr. Okada's (Medical Officer) and Dr. Buenconsejo's (Biostatistics) reviews for details.

Table 2.2.2.2. Percentage of ACR responders in 5 Phase 3 studies.



Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment					
Study	**Pbo + MTX**	**TCZ 4mg/kg + MTX**	**TCZ 8mg/kg + MTX**	**p-value (4 mg/kg)**	**p-value (8 mg/kg)**
WA17822	(n=204)	(n=213)	(n=205)		
ACR20	26	48	58	<0.0001	<0.0001
ACR50	11	32	44	<0.0001	<0.0001
ACR70	2	12	22	<0.0001	<0.0001
WA17823	(n=393)	(n=399)	(n=398)		
ACR20	27	51	56	<0.0001	<0.0001
ACR50	10	25	32	<0.0001	<0.0001
ACR70	2	11	13	<0.0001	<0.0001
WA18062	(n=158)	(n=161)	(n=170)		
ACR20	10	30	50	<0.0001	<0.0001
ACR50	4	17	29	<0.0001	<0.0001
ACR70	1	5	12	0.1005	0.0002

Study	**Pbo + DMARD**	**TCZ 8mg/kg + DMARD**	**p-value (8 mg/kg)**
WA18063	(n=413)	(n=803)	
ACR20	24	61	<0.0001
ACR50	9	38	<0.0001
ACR70	3	20	<0.0001

Study	**MTX**	**TCZ 8 mg/kg**	**Tx Diff**	**95% CI**	**p-value**
WA17824	(n=284)	(n=286)			
ACR20	52	70	0.19	(0.11,0.27)*	<0.0001
ACR50	34	44	0.12	(0.04,0.20)	0.0023
ACR70	15	28	0.14	(0.88,27.59)	0.0002

*Non-inferiority demonstrated if lower limit of 95% CI MRA minus MTX ≥ -0.12

Safety:

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions (occurring in ≥ 5% of patients treated with ACTEMRA monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT. Decreases in neutrophil counts and elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed in patients receiving TCZ. Tables 2.2.2.3 and 2.2.2.4 list incidence rates of various events.

Table 2.2.2.3.

Exposure and Exposure Adjusted Incidence Rates for Deaths, SAEs, SIEs, and Malignancies in the Tocilizumab RA Pivotal Studies and Long-Term Extensions							
	6-months pooled safety population						Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2439
Total patient-years exposure	462	123	321	685	126	1131	2628
Deaths, n (%)	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	11 (0.5)
Deaths per 100 pt-yrs	0.9	0.8	0	0.3	2.4	0.4	0.4
Malignancies, n (%)	7 (0.6)	3 (1)	5 (0.6)	10 (0.6)	2 (0.7)	17 (0.6)	39 (1.6)
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.5
SAEs, n (%)	75 (6)	15 (5)	51 (7)	115 (7)	12 (4)	178 (7)	334 (14)
SAEs per 100 pt-yrs	16	12	16	17	10	16	13
SIEs, n (%)	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	93 (3.8)
SIEs per 100 pt-yrs	3.7	1.6	4.0	5.5	3.2	4.9	3.5

* Includes MTX
Data cut-off April 20, 2007
Adapted from Tables 12, 13, 23, 26 and 38 of Module 2.7.4 Summary of Clinical Safety and source tables STae_py_mal and STrate_ae_s

Table 2.2.2.4. Common AE.

	Placebo + DMARD* n = 1170 n (%)	MTX n = 284 n (%)	MRA 4mg/kg + MTX n = 774 n (%)	MRA 8mg/kg + DMARD* n = 1582 n (%)	MRA 8mg/kg n = 288 n (%)	All MRA n = 2644 n (%)
Total Pts, > 1 AE	359 (31)	117 (41)	279 (36)	618 (39)	135 (47)	1032 (39)
Total No. AEs	489	164	401	904	201	1506
Infections/Infestations	206 (18)	56 (20)	132 (17)	326 (21)	60 (21)	518 (20)
GI Disorders	101 (9)	57 (20)	81 (10)	160 (10)	46 (16)	287 (11)
Nervous System Disorders	59 (5)	11 (4)	57 (7)	124 (8)	28 (10)	209 (8)
Vascular Disorders	32 (8)	6 (2)	32 (4)	70 (4)	16 (6)	118 (4)
Laboratory/Investigations	10 (1)	11 (4)	22 (3)	50 (3)	16 (6)	88 (3)
Skin and Subcutaneous	15 (1)	4 (1)	30 (4)	52 (3)	7 (2)	89 (3)
Musculoskeletal	28 (2)	3 (1)	16 (2)	52 (3)	7 (2)	75 (3)

*includes MTX

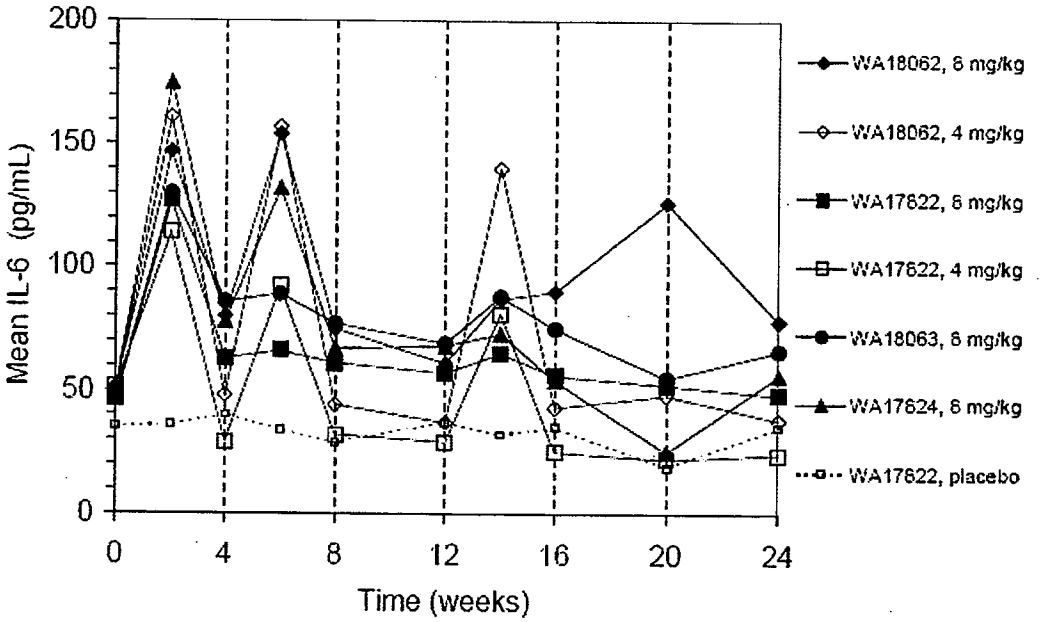
Infections: URI, nasopharyngitis, bronchitis, UTI, sinusitis
GI disorders: Nausea, diarrhea, dyspepsia, abdominal pain
Nervous system disorders: Headache, dizziness
Vascular disorders: Hypertension
Laboratory/Investigations: ALT increased
Skin and subcutaneous: Rash
Musculoskeletal: Back pain

2.2.3 What pharmacodynamic markers were evaluated?

IL-6, sIL-6R, and C-reactive protein (CRP) were monitored in multiple studies as PD indicators. IL-6 and sIL-6R are directly linked to the mechanism of action of tocilizumab. CRP is synthesized by hepatocytes as a direct effect of IL-6 signaling in response to proinflammatory cytokines, in particular IL-6. CRP is used in the diagnosis of RA and is also included in the disease core set DAS28.

IL-6:

Following administration of tocilizumab, IL-6 levels initially increased and then generally decreased with time. IL-6 trough levels were close to baseline for 4 mg/kg tocilizumab, but were about 1.4- to 2.5-fold above baseline for 8 mg/kg tocilizumab (Figure 2.2.3.1).

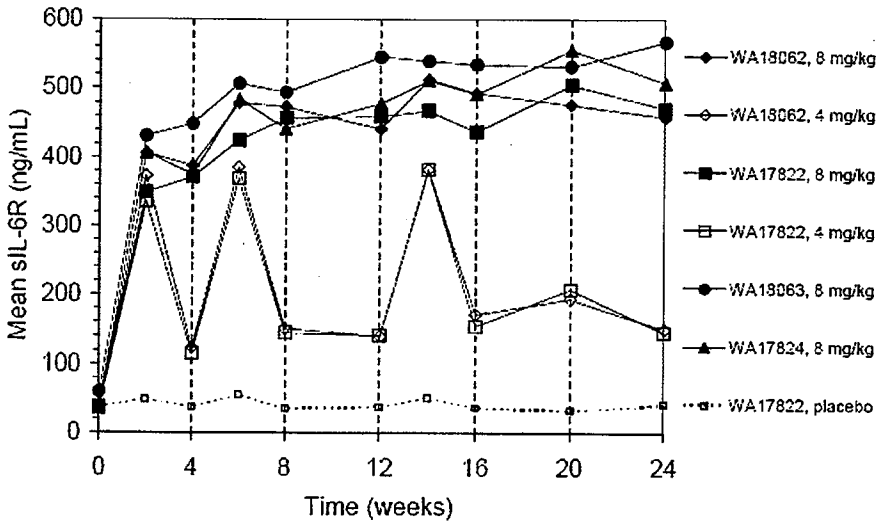


Vertical lines indicate dosing interval; for SEM refer to plots of individual studies; only for study WA17822 are placebo+DMARD data included; IL-6 data comprised only data from the low sensitivity assay, data from the high sensitivity assay were not included

Figure 2.2.3.1. Mean IL-6 Levels in Patients Treated with 4 and 8 mg/kg Tocilizumab every 4 Weeks in Four Phase 3 Studies (WA17822, WA17824, WA18062 and WA18063).

sIL-6R:

Following administration of TCZ 8 mg/kg every 4 weeks, high and sustained sIL-6R levels were observed with only a slight fluctuation within the dosing interval (Figure 2.2.3.2). Total sIL-6R concentrations represent sIL-6R bound to tocilizumab as long as tocilizumab concentrations are ≥ 1 µg/mL (study MRA002JP).

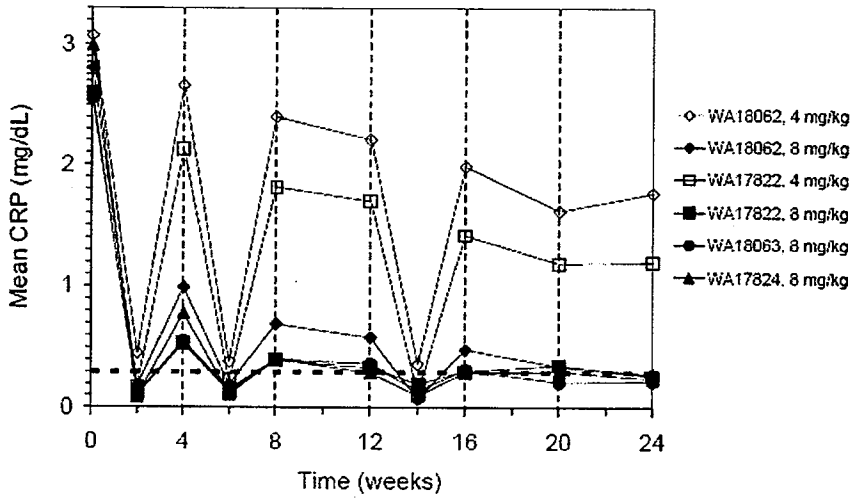


Vertical lines indicate dosing interval; for SEM refer to plots of individual studies; only for study WA17822 are placebo+DMARD data included

Figure 2.2.3.2. Mean sIL-6R Levels in Patients Treated with 4 and 8 mg/kg Tocilizumab every 4 Weeks in Four Phase 3 Studies (WA17822, WA17824, WA18062 and WA18063).

CRP:

For 8 mg/kg every 4 weeks, CRP levels were markedly suppressed as early as week 2 and sustained around the normal range during the dosing interval. Only slight fluctuations in CRP were observed with this dose. For multiple doses of 4 mg/kg every 4 weeks, fluctuations in CRP levels were greater than those with 8 mg/kg (Figure 2.2.3.3).



Dotted horizontal line: upper limit of reference range; vertical lines indicate dosing interval

Figure 2.2.3.3. Mean CRP Levels in RA Patients Treated with 4 and 8 mg/kg Tocilizumab every 4 Weeks in Four Phase 3 Studies (WA17822, WA17824, WA18062 and WA18063).

2.2.4 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Concentrations of tocilizumab were determined in human serum samples with validated sandwich enzyme immunoassays (EIA). See Section 2.6.1.

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

Dose Selection: Two Phase 2 studies were conducted that studied doses of 2, 4, and 8 mg/kg every 4 weeks in RA patients with and without MTX. Based on the outcome, 4 and 8 mg/kg were selected for studying in Phase 3 studies.

Phase 2 dose-finding studies:

• **Study LRO301** was a 20-week Phase 2, double-blind, parallel-group, placebo-controlled, randomized, seven-arm, dose-finding study conducted in Europe, with TCZ given alone or in combination with MTX. This was the primary study used to support the doses investigated in the pivotal trials.

• **Study MRA009JP** was a 12-week Phase 2, double-blind, placebo-controlled, randomized, dose-finding study conducted in Japan with TCZ given alone.

	MRA009JP	LR0301
Design	Phase II, randomized, double-blind, parallel group	Phase IIb, randomized, double-blind, placebo-controlled parallel group
Patient Population	Japanese RA patients with an inadequate response to current DMARD/ immmmosuppressant therapy	European RA patients with an inadequate response to MTX
Treatment	3-arm study: Tocilizumab alone: 4 or 8 mg/kg or placebo iv every 4 weeks	7-arm study: Tocilizumab alone: 2, 4 or 8 mg/kg tocilizumab – MTX; 2, 4 or 8 mg/kg or placebo – MTX iv every 4 weeks
Total No Patients	163	359
Primary Endpoint	ACR20 response at week 12	ACR20 response at week 16

Results from Study LRO301 showed that the percentage of patients achieving the ACR20 response criteria increased with increasing duration of exposure to the study treatment and increasing dose of MRA within the monotherapy and combination therapy groups (Figure 2.2.5.1). TCZ (MRA) 8 mg/kg was the most efficacious dose as monotherapy and MRA 8 mg/kg + MTX was the most efficacious combination dose. There was a statistically significant linear dose-response for the ACR 20 response rate. ACR 20 response rate at Week 16 LOCF is presented in Figure 2.2.5.2 (this figure also includes ACR 50 and ACR 70).

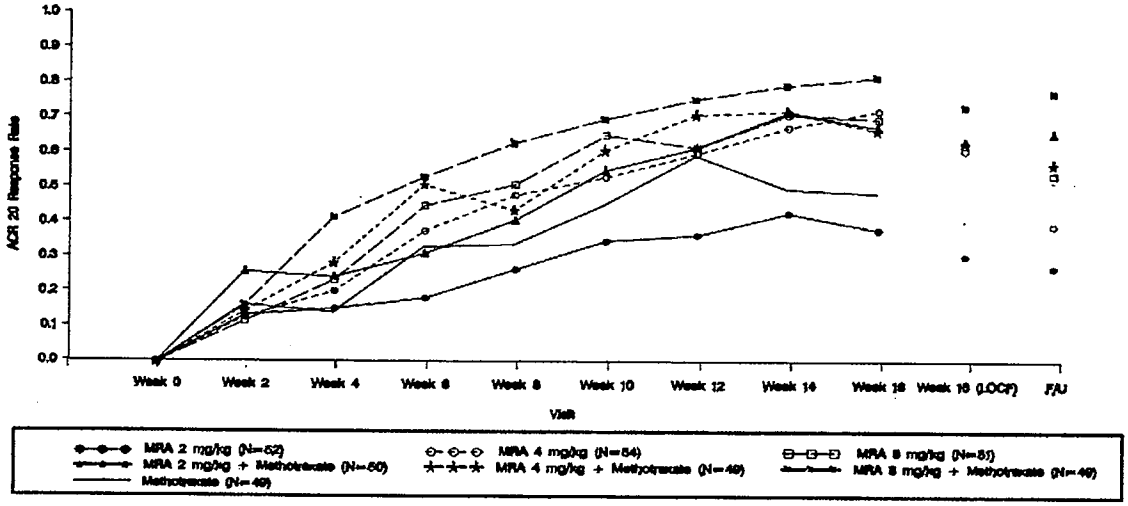


Figure 2.2.5.1. ACR20 Response Rate Over Time.

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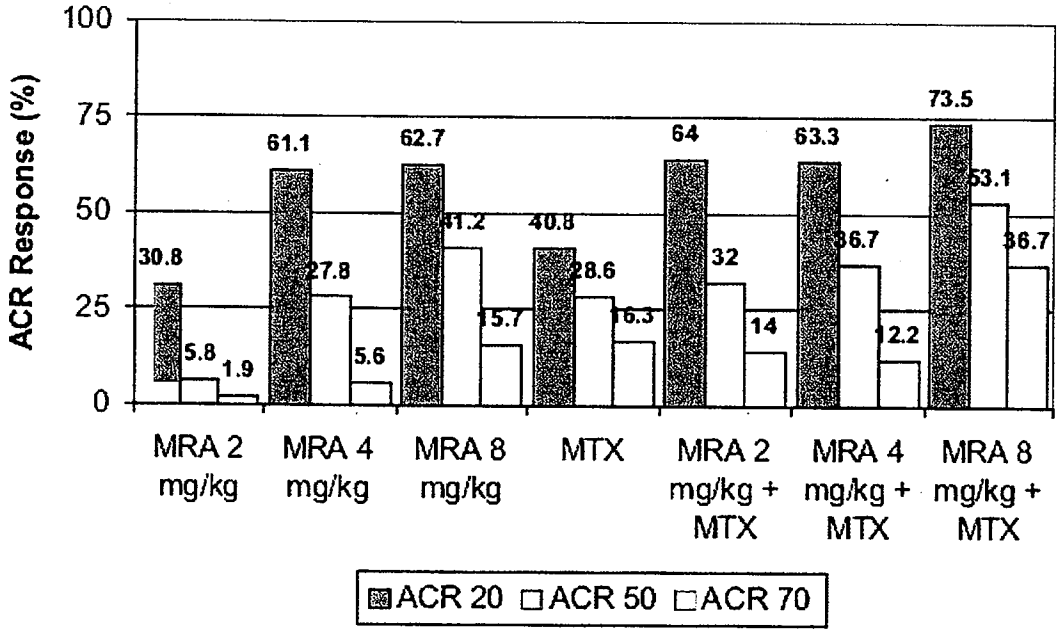


Figure 2.2.5.2. ACR Response Rate at Week 16 (LOCF).

Exposure-Response for Efficacy: Both 4 and 8 mg/kg every 4 week doses showed statistically significant ACR20 response compared to placebo. A higher proportion of patients achieved ACR20 under 8 mg/kg dose than 4 mg/kg dose (Table 2.2.2.1). In addition, a sustained decrease in CRP throughout treatment duration was achieved at 8 mg/kg every 4 week dose but not at 4 mg/kg dose (Figure 2.2.3.3).

Exposure-Response for Safety:
The sponsor conducted additional analysis to evaluate if the higher AUC, Cmax, Cmin resulted in higher safety related events. Figure 2.2.5.3 shows the plot of serious adverse events (SAEs) super classes versus the AUC of tocilizumab cumulated up to the time of occurrence of SAEs in patients treated with tocilizumab. Based on visual examination of the figure it appears that there is no clear link between higher exposures and the safety events.

Although there is no clear relationship of safety with regard to dose or exposure, the 4 mg/kg dose of tocilizumab appeared to be associated with a lower incidence of serious infection than the 8 mg/kg dose when used in combination with a DMARD; no GI perforation events were reported in patients on 4 mg/kg. In the 24 week controlled period, 3 GI perforations occurred in patients on TCZ 8 mg/kg in vs. none on placebo or 4 mg/kg. The July 29 AC meeting will discuss whether 4 mg/kg should be recommended for certain patient sub-populations.

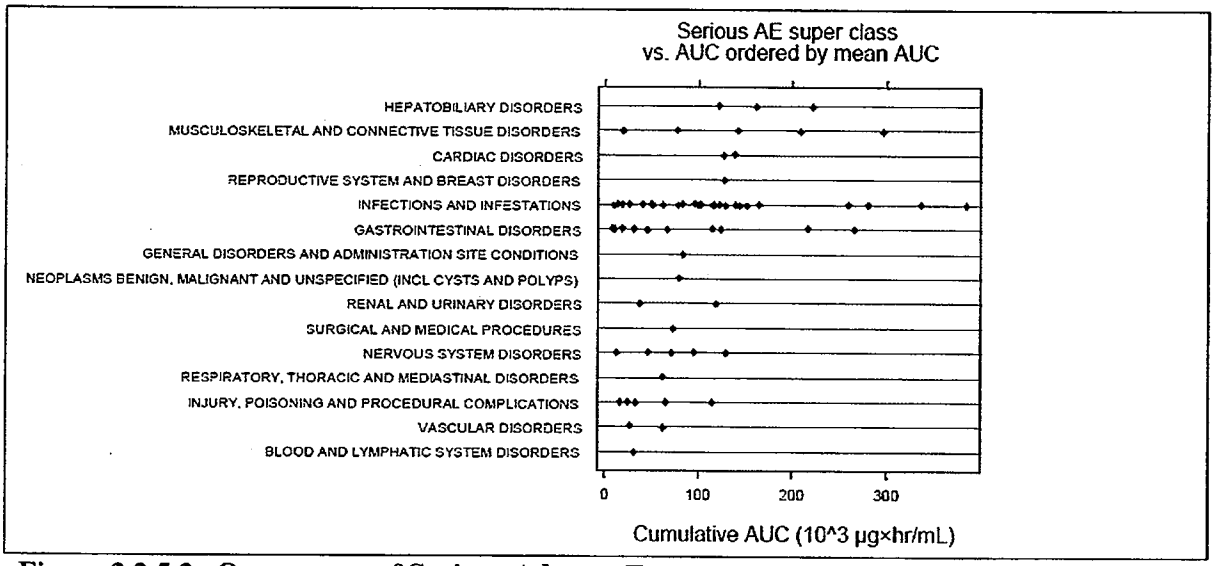


Figure 2.2.5.3. Occurrence of Serious Adverse Events versus cumulative AUC of tocilizumab.

2.2.6 What are PK characteristics of tocilizumab in healthy subjects? Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The PK of tocilizumab was studied in both healthy subjects and RA patients after single doses. PK has also been evaluated in RA patients after multiple dosing. PK of TCZ is nonlinear over the dose range tested. Clearance was concentration-dependent at lower doses. For antibodies such as tocilizumab, there are two types of elimination mechanisms: the nonspecific linear clearance by the reticuloendothelial system and the antigen-mediated saturable clearance.

Data from Study 19461 Part 1 showed that CL decreased with increased dose (2 to 28 mg/kg). Mean CL was estimated as 0.609 mL/h/kg for the 2 mg/kg dose and decreased with increasing doses to 0.192 mL/h/kg for the highest dose of 28 mg/kg. Mean apparent $t_{1/2}$ ranged from 54 h after 2 mg/kg to 293 h (12 days) after 28 mg/kg. Mean V_{ss} ranged from 50.0 (2 mg/kg) to 85.7 mL/kg (20 mg/kg) (Table 2.2.6.1 and Figure 2.2.6.1). Dose of 8 mg/kg was not studied. Mean apparent $T_{1/2}$ at 10 mg/kg was 201 hours (8 days).

Table 2.2.6.1. Summary of Mean1 (CV%) Pharmacokinetic Parameters of Tocilizumab in Serum by Dose Group.

Parameter	2 mg/kg N = 5	10 mg/kg N = 6	20 mg/kg N = 10	28 mg/kg N = 5
C_{max} (µg/mL)	41.9 (8%)	242 (13%)	410 (20%)	558 (14%)
t_{max} [2] (h)	4 (1-8)	4 (2-8)	3 (1-8)	4 (1-4)
AUC_{inf} (h*µg/mL)	3310 (11%)	42300 (19%)	97300 (24%)	147000 (12%)
AUC_{last} (h*µg/mL)	3210 (13%)	37800 (16%)	77800 (22%)	115000 (9%)
$t_{1/2}$ (h)	54.0 (20%)	201 (15%)	277 (13%)	293 (16%)
MRT_{inf} (h)	82.1 (7%)	282 (18%)	401 (14%)	428 (17%)
V_{ss} (mL/kg)	50.0 (13%)	67.5 (14%)	85.7 (24%)	81.4 (14%)
V_z (mL/kg)	47.4 (23%)	69.5 (12%)	85.3 (21%)	80.5 (13%)
CL (mL/h/kg)	0.609 (10%)	0.243 (17%)	0.217 (24%)	0.192 (11%)

[1] Values reported as arithmetic means.
[2] Median values (min-max) reported for t_{max}.

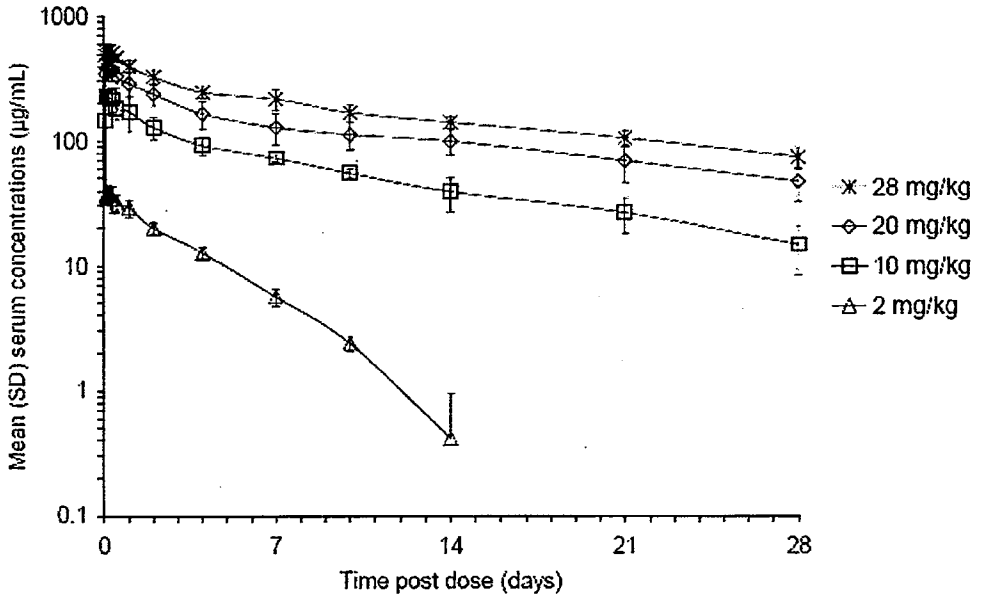


Figure 2.2.6.1. Arithmetic Mean (± SD) Serum Concentration-Time Profiles of Tocilizumab by Dose Group.

2.2.7 What is PK of tocilizumab in RA patients? How does the PK of tocilizumab in healthy volunteers compare to that in RA patients?

Single dose (Study LRO300):
Single dose PK parameters for TCZ in RA patients from Study LRO300 is shown in Table 2.2.7.1.

Table 2.2.7.1.

Table 11 Mean (±SD) Pharmacokinetic Parameters of MRA in Patients with RA Following a Single 1 hour Infusion of MRA

Pharmacokinetic Parameter	MRA			
	0.1 mg/kg	1.0 mg/kg	5.0 mg/kg	10.0 mg/kg
C_{max} (µg/ml)	1.96 (1.26)	17.9 (4.7)	123 (21)	273 (121)
T_{max} (hours)	1.192	4.000	1.183	4.250
AUC_t (µg/hour/ml)	18 (13)	1177 (839)	18093 (3531)	43560 (17032)
AUC (µg/hour/ml)	- (-)	1608 (-)	19504 (3062)	46099 (18249)
$t_{½}$ (hours)	-	52.9	135.9	158.0
CL (ml/hour/kg)	- (-)	0.74 (-)	0.26 (0.04)	0.26 (0.13)
V_z (ml/kg)	- (-)	54.7 (-)	51.4 (6.2)	56.9 (13.6)
MRT (hours)	- (-)	70.5 (-)	193.2 (39.9)	242.7 (53.1)
V_{ss} (ml/kg)	- (-)	49.7 (-)	49.7 (7.5)	58.7 (22.4)

Source data are contained in the Pharmacokinetic Report; see Appendix 16.1.14.

Multiple Doses:
POP-PK analysis was conducted based on data obtained from 4 Phase 3 studies. Concentration-dependent CL was described by the PK model where total CL is the sum of both linear (concentration-independent) and non-linear (concentration-dependent) CL. The nonlinear elimination pathway of tocilizumab possibly represents a target mediated clearance process due to the binding to IL-6R. The dependence of total clearance on tocilizumab serum concentrations, using population estimates of the linear (CL) and the nonlinear clearance (serum tocilizumab concentration ×VM/KM) components, is shown in Figure 2.2.7.1. The two components of the total clearance contribute equally to the elimination of tocilizumab for concentrations around 25 µg/mL. Mean linear CL was 0.18 mL/h/kg (12.5 mL/h). The average contribution of the nonlinear (concentration dependent) CL to the total CL was less at 8 mg/kg than at 4 mg/kg tocilizumab every 4 weeks. The time to steady state, accumulation ratio for Cmax, Cmin and AUC were determined using simulations. The estimated parameters after single and multiple doses are shown in Table 2.2.7.2.

PK parameters estimated from the model are listed in Table 2.2.7.2.

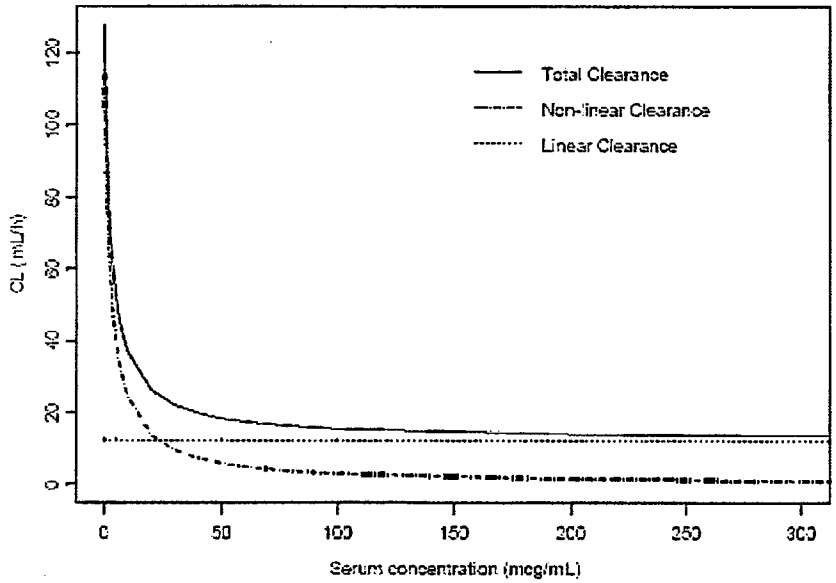


Figure 2.2.7.1. Relationship between Total Clearance, Nonlinear Clearance and Linear Clearance and Tocilizumab Serum Concentrations (Based on Final POP-PK Estimates).

Table 2.2.7.2. Summary of Mean (± SD) Predicted AUCτ, Cmax and Cmin for the First Dosing Interval and at Steady-State following 4 and 8 mg/kg Tocilizumab every 4 Weeks.

Pharmacokinetic Parameter	4 mg/kg every 4 weeks			8 mg/kg every 4 weeks		
	First Dosing Interval	Steady-State	R_{AC}	First Dosing Interval	Steady-State	R_{AC}
AUC_τ (h·µg/mL)	11800 ± 5000	13000 ± 5800	1.11	28800 ± 11600	35000 ± 15500	1.22
C_{max} (µg/mL)	86.8 ± 40.9	88.3 ± 41.4	1.02	174 ± 81.9	183 ± 85.6	1.06
C_{min} (µg/mL)	0.76 ± 0.91	1.49 ± 2.13	1.96	4.14 ± 4.29	9.74 ± 10.5	2.35

R_{AC}: accumulation ratio; a simulation experiment was performed with 48 weeks of treatment and the two doses tested in Phase III (4 and 8 mg/kg every 4 weeks) with 10 studies (replicates) (n = 1793 patients per replicate); AUCτ: AUC within dosing interval

The PK of tocilizumab were similar in HV and in RA patients based on the comparison of non-compartmental PK data from study BP19461 in HV, Study LRO300 in RA, and mean estimates from the popPK analysis in RA patients (Table 2.2.7.3). Because of the concentration-dependent CL, the comparison of PK data between HV and RA patients needs to be based on the same dose level. Therefore, the popPK model was used to predict AUC_{inf} and C_{max} for doses of 2 and 10 mg/kg. For Cmin, similar mean (± SD) tocilizumab serum concentrations were observed at 4 weeks post-dose, being 14.8 ± 6.3 µg/mL (n = 6) and 11.6 ± 9.1 µg/mL (n = 7) for HV and RA patients (studies BP19461 and LRO300, respectively).

Table 2.2.7.3. Summary of Main Mean (± SD) Pharmacokinetic Parameters of Tocilizumab in Serum by Dose Group in Healthy Volunteers and RA Patients.

Study	Study Population	N	AUC_{inf} (µg·h/mL)		C_{max} (µg/mL)	
			2 mg/kg	10 mg/kg	2 mg/kg	10 mg/kg
PK single dose data (BP19461)	HV	5-6	3310 (367)	42300 (7980)	41.9 (3.33)	242 (31.3)
PK single dose data (LRO300)	RA patients	7	-	46100 (18200)	-	273 (121)
PopPK estimates (single dose)	RA patients	1793	4690 (2180)	39600 (16300)	43.3 (21.0)	217 (105)

HV: healthy volunteers; RA: rheumatoid arthritis

The $T_{1/2}$ of tocilizumab is concentration-dependent. The apparent $T_{1/2}$ was estimated to be from 10 to 19 days for 8 mg/kg every 4 weeks at steady-state corresponding to Cmin and Cmax, respectively. The effective $T_{1/2}$ was estimated to be 4-13 days. Half-life under multiple doses was not characterized with dense sampling.

See PM Review (Appendix 4.3) for POP-PK related analyses.

2.2.8 What are ADME characteristics of tocilizumab in animals?

No radiolabeled ADME study for TCZ was conducted in human. Tissue distribution studies in rats and in cynomolgus monkeys showed a low tissue penetration, with low tissue/plasma ratios

in both species. Tocilizumab was, however, shown to distribute to the articular sites of pharmacological activity for the treatment of RA, such as synovia and synovial membrane.

Tocilizumab passed the placental barrier in pregnant monkeys, and was detectable in fetal plasma. Metabolism studies in both rats and monkeys revealed that drug-related material in plasma consisted nearly exclusively of intact tocilizumab. In tissues, drug-related material appeared to consist predominantly of TCA-precipitable radioactivity and a small fraction of non-TCA-precipitable radioactivity (i.e., small peptides, amino acids and/or free ^{125}I). Elimination was mainly via the renal route as small peptides, amino acids and/or ^{125}I, with negligible renal elimination of unchanged tocilizumab. The results are consistent with literature on other IgGs, with slow catabolism being a consequence of recycling via the FcRn receptor. When catabolism eventually occurs, it is via cleavage in lysosomes to small peptides or amino acids.

The excretion of tocilizumab in milk has not been studied. However, it is well established in rodents that IgG is excreted in milk and transferred to the suckling offspring via the FcRn receptor in the small intestine. Therefore, milk excretion of tocilizumab similar to other IgG appears probable in rodents.

Refer to Dr. Mukherjee's (Pharm/Tox) review for details.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Although no specific studies were conducted, based on the results of the POP-PK analyses, age, gender, race and ethnicity had no impact on the PK of tocilizumab in adult RA patients (Figures 2.3.1.1, 2.3.1. 2 and 2.3.1.5). Refer to PM review (Appendix 4.3) for POP-PK and covariate analyses.

a) Gender

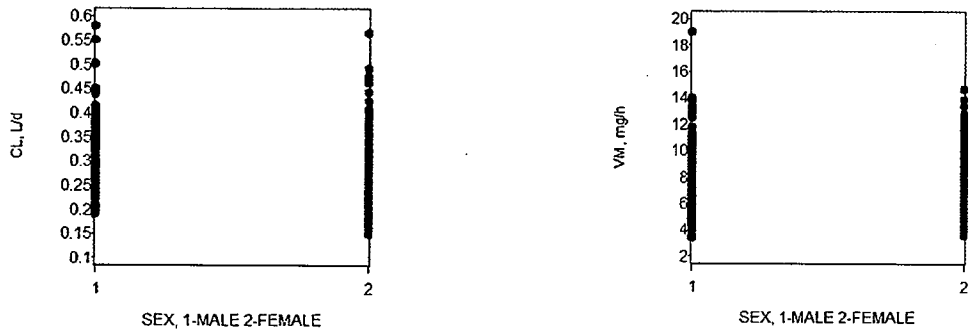


Figure 2.3.1.1. Relationship between clearance (linear) and VM (Maximum elimination rate, nonlinear) and sex.

b) Elderly

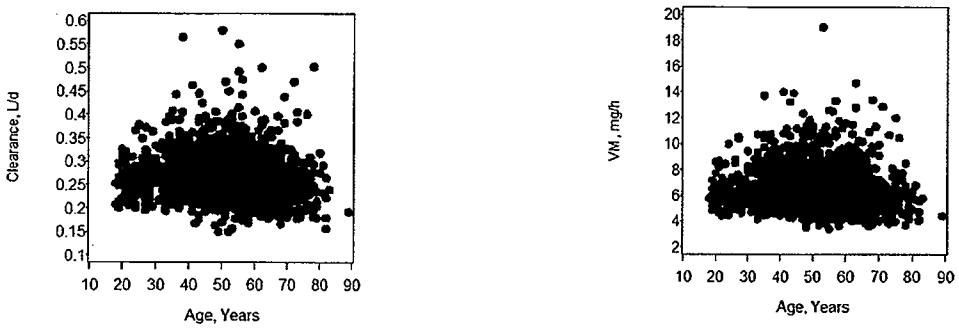


Figure 2.3.1.2. Relationship between clearance (linear) and VM (Maximum elimination rate, nonlinear) and age.

c) Pediatric Patients

The Sponsor requested a deferral for studying safety and efficacy in pediatric patients. Studies with tocilizumab have been conducted in pediatric patients in 2 juvenile idiopathic arthritis (JIA) indications: pJIA (polyarticular) and sJIA (systemic) (Table 2.3.1.1). The Sponsor will undertake additional studies in both pJIA and sJIA to further characterize the PK in these pediatric patient populations.

Table 2.3.1.1.

Indication	Study Number/ Phase	Study Ref.	No. of Patients	Doses (mg/kg) (No. of Patients)	Dosing Frequency	Treatment Duration
sJIA	LRO320 I/II	[7520] lro320.pdf -1	18	2, 4, 8 (n = 6 each)	Single dose	
	MRA011JP II	[7517] mra011jpmain.pdf -1	11	2 (n = 3) 4 (n = 5) 8 (n = 3)	2 weeks	3 infusions at final dose. individual escalation
	MRA316JP III	[7519] mra316jp.pdf -1	56	8	2 weeks	3 infusions followed by 6 infusions
pJIA	MRA318JP III	[7516] mra318jp.pdf -1	19	8	4 weeks	3 infusions

d) Body Weight

In the POP-PK analysis, linear CL was found to increase with body size (Figure 2.3.1.3). Among the 3 body size parameters tested (BW, BSA and BMI), only BSA was retained in the final POP-PK model. In a range of BSA from 1.25 to 2.67 m^2, linear CL was found to change from -20% to +30%. The 3 parameters of body size are highly correlated and the relationship between these covariates and linear CL was similar, especially for BW and BSA.

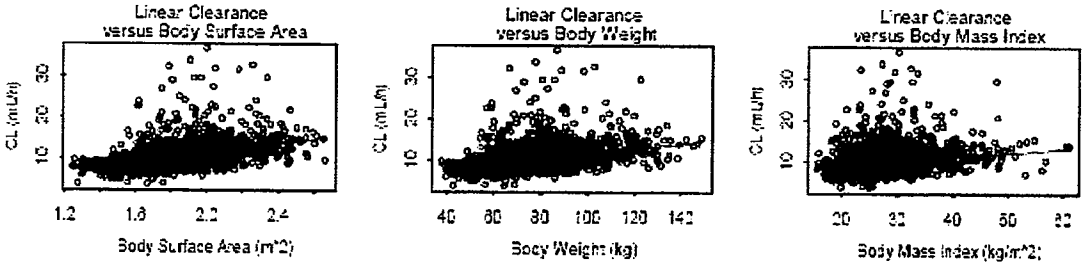
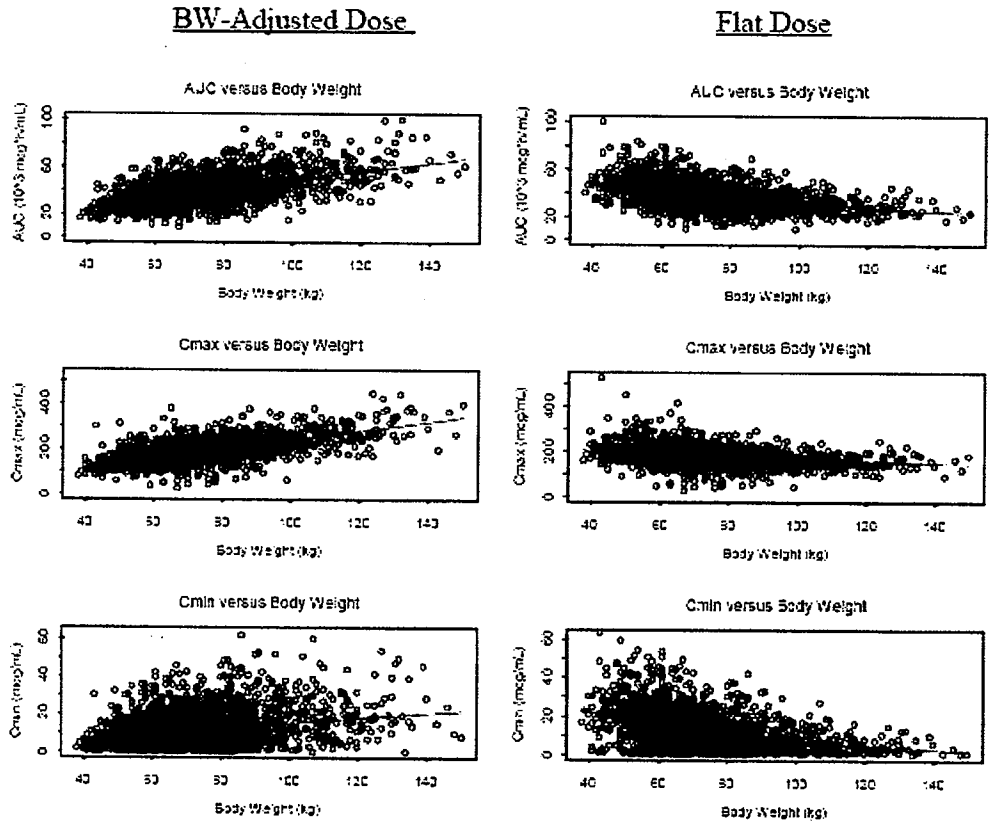


Figure 2.3.1.3. Relationship between Linear CL and BSA, BW and BMI.

With a flat dose, an increase in BW would result in a decrease in the secondary PK parameters AUC and C_{min} (Figure 2.3.1.4, right panel). With a BW-adjusted dosing regimen the effect of BW on CL is accounted for. However, this BW adjustment resulted in a slightly higher exposure with higher BW (Figure 2.3.1.4, left panel).



* The flat dose of 560 mg was calculated based on a median BW of 70 kg

Figure 2.3.1.4. Comparison of the Relationship Between BW and the Steady-State Tocilizumab Secondary Posthoc PK Parameters (AUC, Cmax and Cmin) with a BW-Adjusted Dose (8 mg/kg - Left Panel) and with a Flat Dose (560 mg* - Right Panel).

Although patients with higher body weight resulted in higher exposure for TCZ, they did not show better efficacy but slightly worse efficacy (Figure 2.3.1.5). In terms of effectiveness ACR20 response to TCZ 8 mg/kg + DMARD decreased slightly with increasing body weight ACR20 response rates were 65%, 58% and 50%, respectively, in the <60 kg, 60-100 kg, >100 kg subgroups. A similar effect was observed in the TCZ 4 mg/kg + DMARD group in an analysis by weight. The number of ACR20 responders was lower in patients >100 kg (26% vs. 51%-55% in the lower weight categories).

A trend towards higher occurrence of any adverse event in patients who weigh more than 100 kg is seen in 8 mg/kg+DMARD group (Table 2.3.1.2). However, similar trend is also seen in Placebo+DMARD group. As overall rate of AE were similar in comparison to other approved drugs for RA, and higher exposure in patients with higher BW did not result in better efficacy, the proposed dose based on body weight seems acceptable.

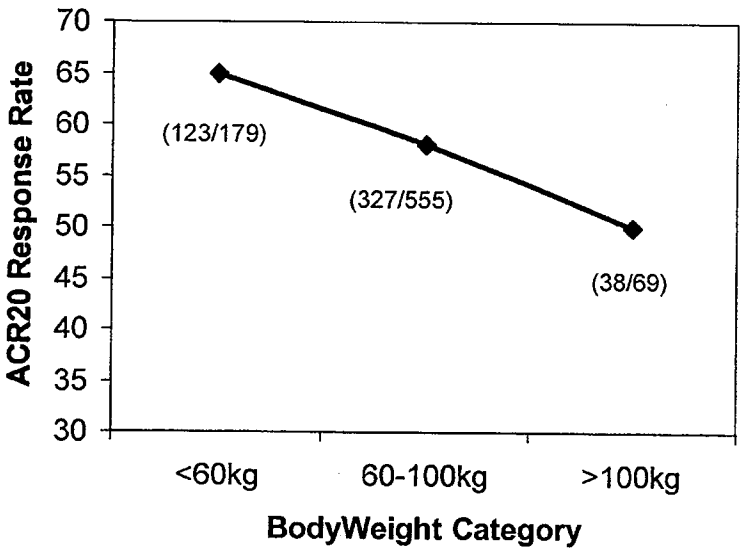


Figure 2.3.1.5. Response Rates in Patients with Different Body Weight Categories after 8 mg/kg Dose (Study WA18063).

Table 2.3.1.2. Overview of Adverse Events by Weight (6 Months Pooled Safety Population).

AE	Placebo +DMARD N=1170	MTX N=284	MRA 4 mg/kg + MTX N=774	MRA 8 mg/kg + DMARD N=1582	MRA 8 mg/kg N=288
N					
> 100 kg	105	28	60	122	22
≥ 60 to ≤ 100 kg	776	181	525	1076	200
< 60 kg	285	74	185	378	63
Missing	4	1	4	6	3
Pts with any AE – n (%)					
> 100 kg	76 (72.4)	19 (67.9)	51 (85.0)	96 (78.7)	19 (86.4)
≥ 60 to ≤ 100 kg	482 (62.1)	136 (75.1)	370 (70.5)	780 (72.5)	153 (76.5)
< 60 kg	173 (60.7)	64 (86.5)	123 (66.5)	254 (67.2)	55 (87.3)
Pts with serious AE – n (%)					
> 100 kg	4 (3.8)	1 (3.6)	2 (3.3)	8 (6.6)	1 (4.5)
≥ 60 to ≤ 100 kg	46 (5.9)	6 (3.3)	30 (5.7)	70 (6.5)	9 (4.5)
< 60 kg	12 (4.2)	1 (1.4)	14 (7.6)	16 (4.2)	1 (1.6)
Pts with AEs leading to WD – n (%)					
> 100 kg	1	2 (7.1)	2 (3.3)	6 (4.9)	-
≥ 60 to ≤ 100 kg	17 (2.2)	10 (5.5)	23 (4.4)	52 (4.8)	8 (4.0)
< 60 kg	10 (3.5)	3 (4.1)	12 (6.5)	15 (4.0)	3 (4.8)
Pts with Infection – n (%)					
> 100 kg	43 (41.0)	10 (35.7)	30 (50.0)	57 (46.7)	9 (40.9)
≥ 60 to ≤ 100 kg	241 (31.1)	62 (34.3)	179 (34.1)	390 (36.2)	65 (32.5)
< 60 kg	90 (31.6)	34 (45.9)	60 (32.4)	143 (37.8)	24 (38.1)
Pts with serious infection – n (%)					
> 100 kg	-	1 (3.6)	1 (1.7)	5 (4.1)	1 (4.5)
≥ 60 to ≤ 100 kg	13 (1.7)	1 (0.6)	7 (1.3)	28 (2.6)	2 (1.0)
< 60 kg	4 (1.4)	-	5 (2.7)	5 (1.3)	1 (1.6)

e) Race

Across the 4 Phase 3 studies, the majority of the patients included in the POP-PK analysis were White (n = 1380, 77%), followed by Asian (n = 150, 8.4%), American Indian or Alaska native (n = 133, 7.4%), Black (n = 64, 3.6%) and others (n = 66, 3.7%). In this analysis, 77% (n = 1386) of patients were of non-Hispanic origin and 23% (n = 407, 23%) were of Hispanic origin.

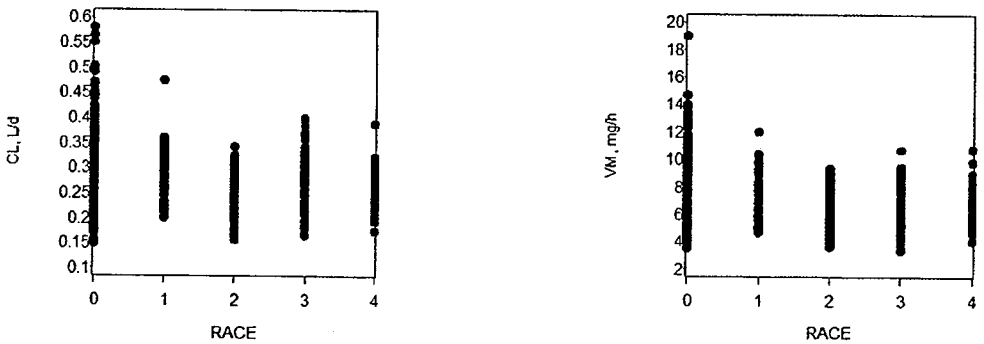


Figure 2.3.1.6. Relationship between clearance (linear) and VM (Maximum elimination rate, nonlinear) and race. RACE=0 refers to White; RACE=1 refers to BLACK, RACE=2

refers to ASIAN, RACE=3 refers to AMERICAN INDIAN or ALASKA NATIVE, RACE=4 refers to Other.

f) Renal and Hepatic Impairment

Monoclonal antibodies of the IgG1 subclass, such as tocilizumab, are thought to be mainly eliminated via proteolytic catabolism in endothelial cells distributed throughout the body. This is in contrast to small molecules, where the elimination is primarily by gastrointestinal/liver metabolism and/or the kidney. Therefore, no formal renal or hepatic impairment studies have been conducted with tocilizumab. As expected from the large molecular size of tocilizumab (approximately 148 000 Da), parent tocilizumab was not excreted in urine to an appreciable amount, indicating that tocilizumab is eliminated primarily via extra-renal pathways.

The Sponsor conducted an exploratory study MRA221JP in patients with mild, moderate and severe renal impairment, no difference in PK was observed between RA patients with and without renal impairment (Table 2.3.1.3).

Table 2.3.1.3. Mean Cmax and AUC based on Renal Fuction.

	Cmax (μg/mL)	AUClast (μg·hr/mL)
Mild (N=4)	174.00 ± 29.14	20,816.00 ± 9334.36
Moderate (N=5)	177.00 ± 18.92	24,796.19 ± 7710.26
Severe (N=3)	172.33 ± 34.95	28,728.73 ± 10,061.85
Normal (N=2)	176.00 ± 25.46	23,417.74 ± 3,472.32

In the POP-PK analysis, creatinine clearance was a statistically significant covariate on VM, ie, the maximum rate of nonlinear CL. Creatinine clearance values ranged from 26.9 to 316.8 mL/min with an effect on VM from -27% to +29%. However, creatinine clearance did not affect AUC and C_{max} for 8 mg/kg, due to the relative small contribution of nonlinear CL to these parameters. There was also no relevant effect observed on C_{min}.

Table 2.3.1.4. Number of RA Patients with Renal Impairment included in the POP-PK Analysis.

Creatinine Clearance (mL/min)	Category of Renal Impairment	Absolute (n) and Relative Number (%) of Patients	
		(n)	(%)
> 80	Normal	1474	82.2%
50 - 80	Mild	290	16.2%
30 - < 50	Moderate	28	1.6%
< 30	Severe	1	0.06%

Creatinine clearance estimated by the Cockcroft-Gault formula

Most patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ≥ 50 mL/min) did not impact the pharmacokinetics of tocilizumab (Figure 2.3.1.7).

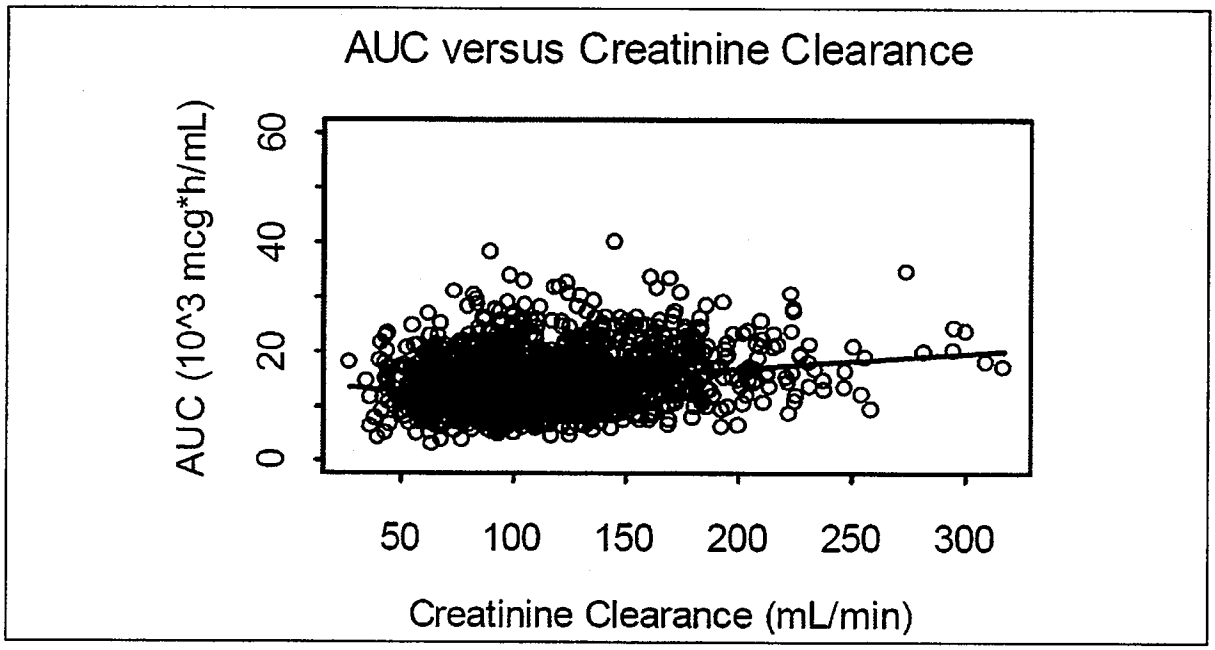


Figure 2.3.1.7. Relationship between AUC and creatinine clearance.

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

Routine samples for anti-TCZ antibody testing were collected at baseline and at months 1, 2, 3, and 6 in the pivotal studies, and every 24 weeks in the long-term extensions. The Sponsor did not collect samples for immunogenicity testing after Week 24 when TCZ levels decreased. In addition to routine testing, patients who experienced an adverse event of "potential immunogenic nature" (defined in the study protocol) or patients who discontinued treatment because of insufficient therapeutic response underwent immunogenicity testing.

A very small proportion of patients tested returned positive for anti-TCZ antibodies (46/2553, 1.8%) in the TCZ treatment groups of the 6-month safety population (all studies). Approximately 6% (10/159) of patients tested for events of potentially immunogenic origin were positive for anti-TCZ antibodies. Five of these patients had events that resulted in withdrawal, to include anaphylactic reaction, infusion reactions, and hypersensitivity. During the 6-month controlled period, fourteen TCZ-treated patients withdrew for reasons ascribed to insufficient therapeutic response and underwent loss of efficacy (LoE) testing; none of these patients were positive for anti-TCZ antibodies. Subsequently, an additional 50 patients have withdrawn for LoE from the long-term extensions; only one of these patients was positive for anti-TCZ antibodies.

In 4 pivotal Phase 3 studies (Studies 17822, 17824, 18062 and 18063), based on the criteria used to determine the development of anti-TCZ HAHAs, a total of 24 out of 1747 (1.4%) patients

developed anti-TCZ HAHAs: 19 patients (1.7%) in the TCZ 8 mg/kg + MTX/DMARD group (including one patient who received TCZ 8 mg/kg open-label treatment as escape therapy), 2 patients (0.7%) in the TCZ 8 mg/kg monotherapy group, and 3 patients (0.8%) in the TCZ 4 mg/kg + MTX group (Table 2.3.2.1). Of the 24 patients who developed anti-TCZ HAHAs (human anti-human antibodies), 9 patients developed antibodies of the Ig class, predominantly IgG or IgM, 18 patients developed neutralizing anti-TCZ HAHAs, and 4 patients developed uncharacterized positive antibodies (screen/confirmation positive). Patients could appear in multiple categories.

Of the 18 patients (1%) who developed anti-TCZ neutralizing HAHAs, 16 were receiving TCZ 8 mg/kg + MTX/DMARD, one was receiving TCZ 4mg/kg + MTX and one was receiving TCZ 8 mg/kg monotherapy. In these 18 TCZ-treated patients, who had detectable neutralizing antibodies, there was no apparent association between neutralizing antibody levels and loss of clinical response. Both CRP levels and DAS28 were either maintained or improved over time, even after neutralizing antibodies were detected, and none of these patients were withdrawn due to lack of therapeutic response.

There does not appear to be any effect of the development of anti-TCZ HAHAs on the frequency or type of infusion-associated adverse event reported.

Six patients in total had 12 adverse events suggestive of an allergic event, meeting the event-driven safety testing criteria after the development of anti-TCZ HAHAs. Only four patients who met the criteria for an event of allergic nature developed anti-TCZ HAHAs prior to the event. One patient had a serious anaphylactic reaction and three patients had an infusion related reaction. One other patient who was screened for anti-TCZ HAHAs had an anaphylactic reaction in the absence of anti-TCZ HAHAs. In certain cases there was a temporal association between the development of anti-TCZ HAHAs and an event of allergic nature which suggests that the assays are capable of detecting anti-TCZ HAHAs in patients with a clinically relevant event.

Table 2.3.2.1. Summary of Patients who were Exposed to Tocilzumab and Developed anti-TCZ HAHAs.

	WA17822		WA18062		WA18063	WA17824	Total
	4 mg/kg + MTX	8 mg/kg + MTX	4 mg/kg + MTX	8 mg/kg + MTX	8 mg/kg + DMARD	8 mg/kg mono	
Safety Population	212	206	163	175	802	288	1846
Patients Tested in the Screening Assay*	202 (95.3)	200 (97.1)	155 (95.4)	167 (95.4)	748 (93.3)	275 (95.5)	1747 (94.6)
Positive Screening and Confirmation Assays (all time points)†	4 (2.0)	7 (3.5)	—	6 (3.6)	19 (2.5)	3 (1)	39 (2.2)
Positive Screening and Confirmation Assay (post-baseline)†	2 (1.0)	5 (2.5)	0	5 (3.0)	9 (1.2)	2 (0.7)	23 (1.3)
Positive antibody (any assay)†¶	2 (1)	5 (2.5)	1 (0.6)	5 (3.0)	9 (1.2)	2 (0.7)	24 (1.4)
Positive neutralizing antibody ‡	1 (0.5)	4 (2)	—	4 (2.4)	8 (1.1)	1 (0.4)	18 (1.0)
Positive [redacted] Antibody ‡	1 (0.5)	1 (0.5)	1 (0.6)	2 (1.2)	3 (0.4)	1 (0.4)	9 (0.5)

b(4)

*Patients screened are expressed as a % of patients treated in the safety population.
†Patients with positive assay or antibody results are expressed as % of patients tested in the screening assay.
‡One patient (5206) had a negative Screening and Confirmation assay result, but had a positive [redacted] result with an associated therefore classed as having positive IgG and IgM antibodies.
Patients can appear in multiple categories (Screening and Confirmation, Neutralizing, and [redacted]

b(4)

Table 2.3.2.2. Summary of patients in the PK dataset tested positive for anti-tocilizumab (TCZ) human anti-human antibodies (HAHAs) in the confirmation assay by study, by dose and by visit.

Presence of anti-TCZ HAHAs	WA17822		WA17824	WA18062		WA18063
	4 mg/kg	8 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg	8 mg/kg
Total number of Patients	2	3	1	0	5	7
Number of patients per visit						
Week 4		2	1		4	3
Week 8	2	2			1	3
Week 12	1				1	3
Week 20	1					
Week 24		1			3	5

Antibody was detected in patients as early as Week 4. In the POP-PK covariate analysis, HAHAs were not identified as a covariate influencing the PK of tocilizumab. Primary PK parameters derived for patients with positive antitocilizumab HAHAs were graphically compared to those from the remaining patients (Figure 2.3.2.1). There were no appreciable differences observed. However, the relatively small number of samples in which anti-tocilizumab HAHAs were detected may limit the interpretation of these results.

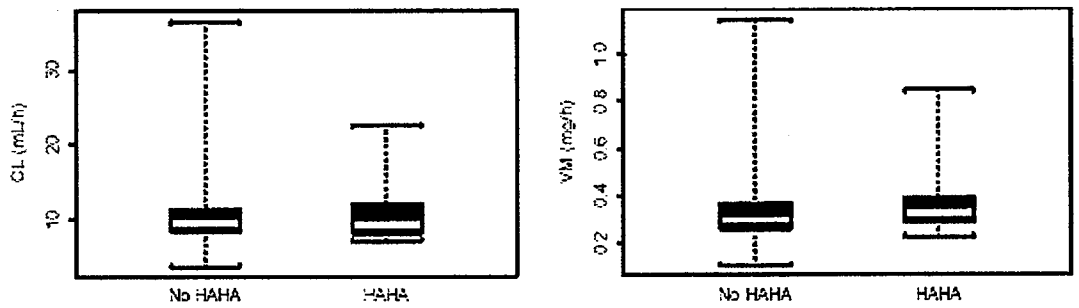


Figure 2.3.2.1. Linear CL (left) and VM (right) for Patients with No HAHAs Detected and for Patients with HAHAs Detected.

Several factors can interfere with the sensitivity and specificity of the assays including the presence of immature IgM, rheumatoid factor, soluble IL-6 receptor levels, auto-antibodies, sample handling, timing of sample collection, concomitant medication, underlying disease, and high concentrations of TCZ. Based on the current assay condition, a small number of samples were tested positive for anti-TCZ HAHAs (1-2%) that may limit the interpretation of the effect of immunogenicity on PK, safety or efficacy. The results indicated that anti-TCZ HAHAs or neutralizing anti-TCZ HAHAs did not appear to affect PK or the evaluated exposure-safety and exposure-efficacy relationship.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

IgG antibodies are not metabolized by P450. Therefore, no direct pharmacokinetic interaction via the CYP pathway is expected between tocilizumab and co-administered small molecular weight drugs. Tocilizumab, however, might indirectly influence the expression level of CYP enzymes in RA patients because IL-6 is known to reduce the expression level of certain CYP enzymes, particularly CYP3A4. Thus, CYP activities may be downregulated in patients with elevated levels of IL-6. Tocilizumab inhibits effects of IL-6, presumably including the CYP downregulatory activities of IL-6. Therefore, because an indirect effect of tocilizumab on the expression levels of CYP enzymes appears to be possible.

Effect of other drugs on tocilizumab:
The potential impact of concomitant drugs for RA on tocilizumab PK was assessed in the covariate analysis of the POP-PK analysis. The results did not show an impact of comedication on tocilizumab PK. Only those drugs that were given at least during 90% of the tocilizumab treatment duration to at least 100 patients were included in the analysis. Concomitant use of MTX, chloroquine and derivatives, immunosuppressants (azathioprine, leflunomide), corticosteroids (prednisone and derivatives), folic acid and derivatives, non-steroidal anti-

inflammatory drugs (diclofenac, ibuprofen, naproxen, meloxicam, cox-2 inhibitors [celecoxib]), and analgesics (paracetamol, codeine and derivatives, tramadol) did not influence the CL of tocilizumab. Figures 2.4.1.1 and 2.4.1.2 showed that MTX or immunosuppressant had no effect on CL or VM (maximum elimination rate of the saturable process) of TCZ.

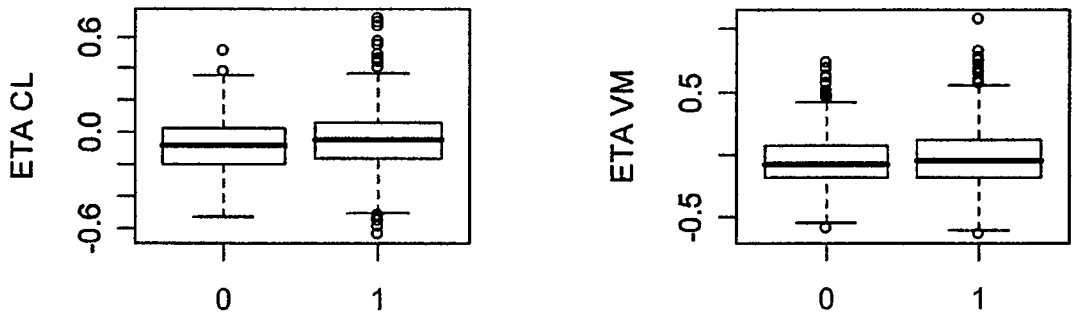


Figure 2.4.1.1. Estimated CL and VM of TCZ in the presence (1) or absence of MTX (0).

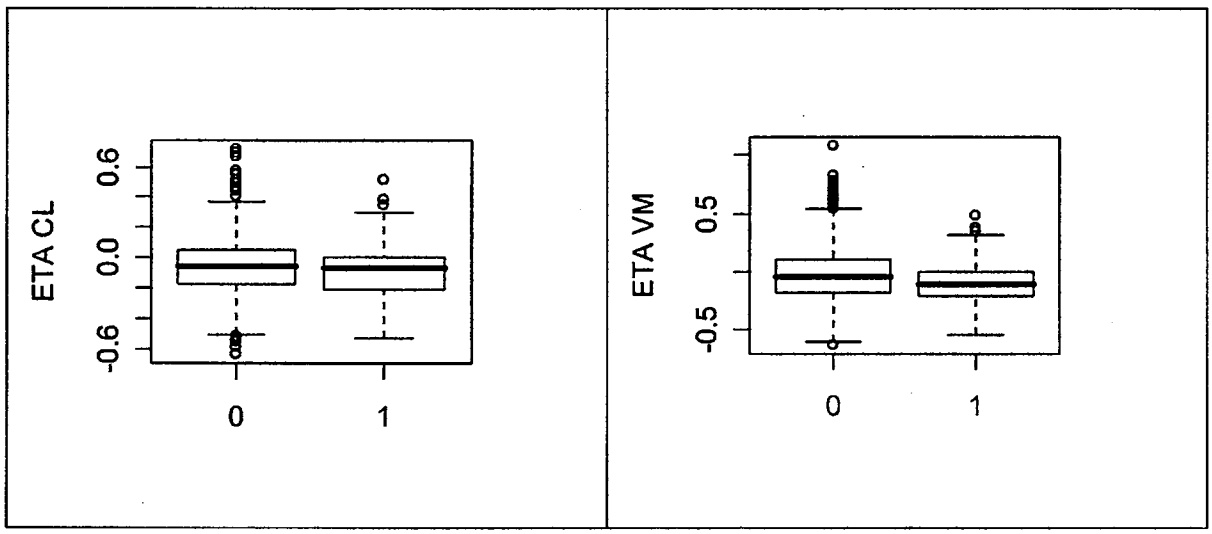


Figure 2.4.1.2. Estimated CL and VM of TCZ in the presence (1) or absence of immunosuppressants (e.g., leflunomide, azathioprine) (0).

Effect of tocilizumab on other drugs:
In an *in vitro* study (Study ADM 03-0155), the expression levels of messenger RNA (mRNA) for various CYP450 enzymes were studied in human hepatocytes after incubation with tocilizumab, IL-6 or a combination of both. In this model system, super-physiological levels of IL-6 reduced mRNA expression for several CYP450 isoenzymes, including CYP3A4, and this reduced expression was prevented by co-incubation with tocilizumab. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may therefore restore CYP450 activities to higher levels than in absence of tocilizumab.

After incubation with IL-6 for 72 hours at 0.5 ng/mL, no marked changes were observed in mRNA expression except that CYP3A4 mRNA levels decreased. At a higher IL-6 concentration

(12.5 ng/mL), mRNA expression for all CYP isoenzymes except CYP2E1 was reduced, most markedly for CYP3A4 (Table 2.4.1.1). Co-incubation with tocilizumab at high concentrations (250 µg/mL) prevented the reduction of mRNA levels for all CYP isoenzymes, while tocilizumab at a low concentration (1 ng/mL) showed no effect.

Table 2.4.1.1. Expression Levels of Cytochrome P450 mRNA in Human Hepatocytes after Incubation with IL-6 and Tocilizumab for 72 h (Levels Relative to Control, Mean ± SD).

Test substance	CYP 1A2	CYP 2B6	CYP 2D6	CYP 2C9	CYP 2C19	CYP 2E1	CYP 3A4
Control	1.00	1.00	1.00	1.00	1.00	1.00	1.00
IL-6 12.5 ng/mL	0.18 = 0.13	0.28 = 0.12	0.67 = 0.28	0.58 = 0.25	0.43 = 0.29	1.28 = 0.58	0.06 = 0.07
Tocilizumab 250 µg/mL and IL-6 12.5 ng/mL	0.76 = 0.23	0.92 = 0.34	0.68 = 0.42	1.44 = 0.63	0.96 = 0.87	0.73 = 0.34	0.95 = 0.82
Tocilizumab 1 ng/mL and IL-6 12.5 ng/mL	0.21 = 0.19	0.28 = 0.15	0.76 = 0.29	0.84 = 0.65	0.29 = 0.29	1.57 = 0.96	0.06 = 0.08

Reviewer's Note: *Monitoring IL-6 levels in clinical studies showed that IL-6 increased following MRA administration. IL-6 levels in RA patients are variable. For example, in Study LRO300 it was determined to be 3.2 to 923.6 ng/mL. High IL-6 concentration (12.5 ng/mL) used in this study could be seen in some RA patients. Cmax for MRA at 8 mg/mL was around 200 µg/mL at steady-state, corresponding to high MRA concentrations used in this study.*

Study 220JP was conducted with dextromethorphan (CYP2D6 and CYP3A4) and omeprazole (CYP2C19). The study results showed that co-administration of tocilizumab 8 mg/kg resulted in a decrease in exposure of omeprazole (~50%) in CYP2C19 extensive metabolizers indicating reverse of downregulation of CYP2C19 (Table 2.4.1.2). Although TCZ showed a little effect on the exposure of dextromethorphan, the exposure of Dextrorphan (a CYP2D6 metabolite of dextromethorphan) level decreased (Table 2.4.1.2). Dextrorphan was metabolized by CYP3A4.

Table 2.4.1.2. Mean (± SD) AUC and Cmax of Dextromethorphan, Dextrorphan and Omeprazole Before and After Tocilizumab Administration of 8 mg/kg (MRA220JP).

Analyte	Parameter	Before Tocilizumab Administration	7 Days After Tocilizumab Administration	Change
Dextromethorphan* **(n = 12)**	AUC_{inf}	14.0 ± 8.8	14.5 ± 11.7	- 4%
	C_{max}	1.97 ± 1.47	1.60 ± 1.22	- 19%
Dextrorphan* **(n = 12)**	AUC_{inf}	31.7 ± 16.4	20.8 ± 9.34	- 34%
	C_{max}	7.89 ± 4.19	4.54 ± 2.02	- 42%
Omeprazole **(n = 8)**	AUC_{last}	844 ± 909	443 ± 704	- 48%
	C_{max}	417 ± 217	212 ± 205	- 49%

Data presented to 3 significant figures; * excluding CYP2D6 poor metabolizer

The Sponsor is conducting a new drug interaction study (Study WP18663) with simvastatin as the CYP3A4 substrate.

It is not clear about the P450 enzyme expression levels in RA patients (who have elevated IL-6) with TCZ compared to those in healthy subjects who have normal IL-6 levels. The P450 expression levels would determine the *in vivo* exposure for a drug that is a P450 substrate. Drug interaction may have clinical implication for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted based on response measurements (e.g., warfarin) or drug monitoring (e.g., cyclosporine or theophylline) where a decrease of up to 50% could become clinically relevant. In addition, depending on the P4503A4 level change, decrease in oral contraceptive (CYP3A4) exposure is expected and may lead to decrease in efficacy.

2.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

2.5 General Biopharmaceutics

2.5.1 What is the final-to-be marketed formulation (drug substance and drug product) of tocilizumab?

The drug substance, tocilizumab, is a colorless to pale yellow liquid with a concentration of approximately —— . (in the G2 to G4 process generations, see Table 2.5.2.1). This concentration is — the limit of solubility for tocilizumab. b(4)

Tocilizumab drug product is supplied as a single formulation in three presentations: 80, 200 and 400 mg. These presentations differ only in volume of solution in the vial (i.e., 4, 10 or 20 mL equivalent to 80, 200 or 400 mg), so that the final concentration of tocilizumab obtained is 20 mg/mL (Table 2.5.1.1). The formulated bulk solution is : —— filled into type I neutral glass vials. Prior to administration, the sterile, liquid concentrate formulation is to be diluted in 0.9% sodium chloride for iv infusion. b(4)

Table 2.5.1.1. Composition of Tocilizumab Drug Product – Summary of all Dosage Strength.

Ingredient	Specification	Quantity/Vial 80 mg	Quantity/Vial 200 mg	Quantity/Vial 400 mg	Concentration (mg/mL)	Function
Tocilizumab	in house specifications	80 mg[c]	200 mg[c]	400 mg[c]	20	Active ingredient
Polysorbate 80	Ph.Eur./USP/JP	2 mg	5 mg	10 mg	0.5	——
Sucrose	Ph.Eur./USP/JP	200 mg	500 mg	1.000 mg	50	——
Disodium phosphate dodecahydrate	Ph.Eur./USP/JP	6.11 mg[d]	15.3 mg[d]	30.5 mg[d]	q.s.[d]	pH buffer
Sodium dihydrogen phosphate dihydrate	Ph.Eur./USP/JPE[b]	6.70 mg[d]	16.8 mg[d]	33.5 mg[d]	q.s.[d]	pH buffer
Total volume adjusted with WFI[a]	Ph.Eur./USP/JP	4 mL	10 mL	20 mL	q.s.	——

b(4)

b(4)

a. Water for Injection.
b. Japanese Pharmaceutical Excipients.
c. May vary dependent on protein content. Calculated on the basis of the actual tocilizumab protein content and actual measurement of tocilizumab drug substance density.
d. pH of solution approx 6.5 and 15 mmol/L for phosphate buffer.

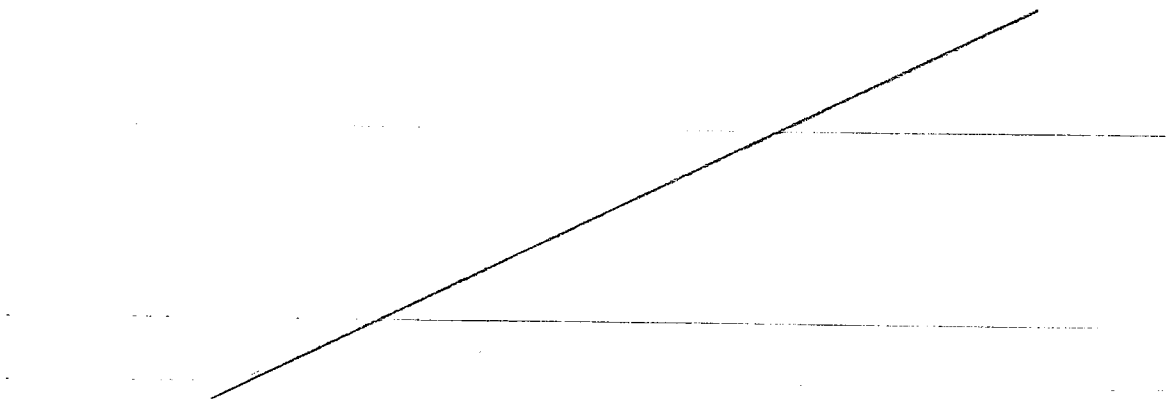
2.5.2 What are the major development processes for drug substance and formulations for drug product? Which batches were used in the pivotal clinical and bioavailability studies?

During the development program of tocilizumab, changes have been made to the manufacturing processes of both drug substance and drug product. These are referred to as 1st generation (G1) to 4th generation (G4) processes for drug substance and DP1, DP2 and DP3 for drug product generations.

Drug Substance:

An overview of the different manufacturing process generations (ie, G1 to G4) is provided in Table 2.5.2.1.

Table 2.5.2.1. Overview of the Different Manufacturing Process Generations for Tocilizumab Drug Substance.



b(4)

G1, G2 and G4 are most relevant to the TCZ application for RA indication in the U.S. Tocilizumab drug substance produced by the G1 process was utilized in nonclinical toxicology studies, as well as, in clinical Phase 1 and 1/2 studies conducted by Chugai in Japan and Europe in adult patients with RA. Tocilizumab drug substance produced by the G2 process was used in Phase 2 studies in Europe. Drug supply derived from the G3 process was used by Chugai for the continuation of clinical programs in Japan and the US (for indications other than RA). Drug supply derived from the G4 process was used by Roche in Phase 1 (BP19461) and Phase 3 studies worldwide and is intended for marketing.

Drug Product:

The initial Phase 1, 2 and 3 studies conducted by Chugai used tocilizumab drug product and drug substance manufactured at the Ukima pilot plant. This drug product is referred to as DP1. Phase 1 and 3 studies conducted by Roche, as well as the continuation of the Chugai clinical program, used drug product manufactured at the Ukima pilot site. This drug product is referred to as DP2. Manufacturing of drug substance used in DP2 was transferred to Utsunomiya, the commercial drug substance manufacturing site, to meet increased demand for clinical supplies. For the ongoing Phase 3 study and the long-term extension studies conducted by Roche, the manufacturing of drug product was also transferred to the Utsunomiya commercial site and this drug product is referred to as DP3.

DP2 (with G4 drug substance) has been used in the pivotal Phase 3 studies. Tocilizumab derived from the G4 and DP3 generations, which has been used in the ongoing Phase 3 study (WA17823) and the long-term extension studies, is intended for commercial supply (Table 2.5.2.2).

Table 2.5.2.2. Tocilizumab Drug Product Generations, their Manufacturing Sites and Use in Clinical Studies.

Drug Product Generation / Formulation	DP1		DP2	DP3
Formulation generation	α, β	γ	γ	γ
Formulation site	Ukima (pilot)	Ukima (pilot)	Ukima (pilot)	Utsunomiya (commercial)
Tocilizumab / vial	100 mg	200 mg	200 mg	80 mg, 200 mg, 400 mg
Drug substance manufacturing facility (Generation)	Ukima (G1)	Ukima (G2 & G3)	Utsunomiya (G4)	Utsunomiya (G4)
Clinical studies in adult RA patients or healthy volunteers, iv administration	Phase I LR0300 MRA001JP MRA004JP Phase I/II MRA002JP	G2: Phase II LR0301 MRA009JP G3: Phase III MRA012JP MRA213JP	Phase I BP19461 MRA220JP MRA221JP Pivotal Phase III WA17822 WA17823 WA17824 WA18062 WA18063 Phase III ext [a] WA18695	Ongoing Phase III WA17823 Phase III ext [a] WA18695 WA18696 foreseen for commercial use

2.5.3 Were various drug products used in clinical studies comparable in terms of PK exposure?

Comparability of the different generations of drug substance and drug product was established using analytical methods and bioassays. No nonclinical or clinical pharmacokinetic (PK) studies were performed to assess the comparability of tocilizumab.

The comparability results from the analytical testing and bioassays are reviewed by the product reviewer, Dr. Feldman. The assessment confirmed that comparability between all generations of drug substance and drug product was established.

Across study comparison of PK data obtained with various drug product generations showed similar PK parameters.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable because TCZ is given via IV infusion.

2.6 Analytical

2.6.1 How were the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Two different validated sandwich enzyme immunoassays (EIA) were used in the clinical studies to determine the concentration of tocilizumab in human serum samples. They are referred to as the Chugai PK assay and the Roche PK assay.

Table 2.6.1.1. Summary of the Different Assays used in the Clinical Studies to Measure Serum Concentrations of Tocilizumab.

Clinical Studies	Tocilizumab Assay	
	PK Assay Chugai	PK Assay Roche
Roche Studies		
BP19461, part 1		X
WP18097[1]	X	
WA17822		X
WA17823[2]		X
WA17824		X
WA18062		X
WA18063		X
WA18695[2]		X
WA18696[2]		X
Chugai Studies[3]		
LRO300	X	
LRO301	X	
MRA001JP	X	
MRA002JP	X	
MRA004JP	X	
MRA009JP	X	
MRA220JP	X	
MRA221JP	X	

Chugai PK assay:

This validated EIA used sIL-6R immobilized onto a 96-well microtiter plate via binding to a murine anti-IL-6R antibody pre-coated to the microtiter plate. The murine antibody has a binding site to IL-6R that is different from that of tocilizumab. Tocilizumab in the samples was captured by sIL-6R and detected by use of a biotinylated goat anti-human IgG (secondary antibody), streptavidin-bound alkaline phosphatase and its substrate (p-NPP: p-nitrophenylphosphate). The lower limit of quantitation (LLOQ) of this early EIA was 1.563 µg/mL (healthy volunteers) or 1.000 µg/mL (RA patients) in whole serum. An ELISA based on the same principle of this assay was developed and validated for human urine specimens (healthy volunteers) with a sensitivity of 15.62 ng/mL.

The assay was cross-validated between the [redacted] b(4)

Table 2.6.1.2. Performance Summary of the Chugai PK Assay.

Validation Site	Assay Range, ng/mL	Accuracy, %		Precision, %	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
[redacted]	1,563 – 25,000 (HV, serum)	106.1 to 122.3	103.1 to 109.4	1.2 to 3.0	7.8 to 14.8
[redacted]	1,000 – 25,000 (RA patients, serum)	75.4 to 81.7	83.6 to 93.5	1.2 to 2.0	11.1 to 19.6
[redacted]	15.62 – 1,000 (HV, urine)	91.9 to 93.8	89.7 to 108.8	2.5 to 10.8	4.9 to 10.0
[redacted]	1,000 – 25,000 (HV, RA patients, serum)	83.2 to 122.0	86.0 to 98.0	5.0 to 30.3	11.8 to 24.7
[redacted]	12 – 2,000 (HV, RA patients, urine)	78.6 to 96.2	74.9 to 89.9	1.2 to 11.4	6.2 to 15.0

HV: healthy volunteers; RA: rheumatoid arthritis

b(4)

Roche PK assay

Roche PK assay is an ELISA developed subsequently to improve the sensitivity of the method for detection of tocilizumab in human specimens. This ELISA is based on the immobilization of sIL-6R onto microtiter plates to capture tocilizumab in the samples. Tocilizumab is detected by a digoxigenin (DIG) labeled antitocilizumab secondary antibody, which in turn, is detected by an anti-DIG horse radish peroxidase (HRP) conjugated antibody and reacts with its substrate. The LLOQ of the ELISA was validated at 0.1 µg/mL. The higher limit of the assay was 3.2 µg/mL. PK samples were diluted with human serum. Dilution QC of various dilution factors were included in the assay.

Assay validation revealed that the measurement of tocilizumab is insensitive to the addition of human IL-6, but is sensitive to the presence of sIL-6R.

The assay was cross-validated between [redacted] It was also cross-validated with the Chugai PK assay. b(4)

Table 2.6.1.3. Performance Summary of the Roche PK Assay.

Validation Site	Assay Range, ng/mL	Accuracy, %		Precision, %	
		Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
____	100 - 3,200	93.8 to 114.5	91.5 to 106.9	0.9 to 4.1	3.9 to 10.4
_____	100 - 3,200	100.6 to 106.0	99.1 to 107.1	1.9 to 10.8	4.8 to 9.8

b(4)

2.6.2 How immunogenicity was determined? What bioanalytical methods were used to detect anti-drug antibodies and those that were neutralizing antibodies in serum or other biological fluids?

Patient sera were first assessed for anti-TCZ HAHAs using a screening assay. Samples testing positive in the screening assay were subjected to confirmatory testing with a confirmation assay. Samples testing positive in both the screening and confirmation assays were subjected to further analysis, designed to provide information on the nature of the antibody detected including the immunoglobulin isotype (IgM, IgG or IgE) and to assess whether the antibody detected was capable of neutralizing the effect of TCZ in vitro.

The immunogenicity testing strategy for tocilizumab followed a two-stage analytical approach, together with clinical event-driven testing, regardless of whether the screening and confirmation assays were positive (Figure 2.6.2.1).

Stage 1: Anti-TCZ HAHA Screening and Confirmation:
The bioanalytical immunogenicity testing in Stage 1 consisted of:
• Testing of the designated patient samples in an anti-TCZ HAHA **screening assay.**
• All samples with a positive screening assay result were then tested in a **confirmation** assay (bridging enzyme-linked immunosorbent assay—ELISA) based on signalsuppression by addition of TCZ in the case of true positives.

Stage 2: Anti-TCZ HAHA Characterization
The bioanalytical testing in Stage 2 consisted of the following standard assays:
• **Inhibition ELISA** to evaluate the potential of anti-TCZ HAHAs to block the binding of TCZ to soluble interleukin-6 receptor (sIL-6R) in an ELISA format indicative of the potential to neutralize the therapeutic effect of TCZ.
• **BiaCore Assay** using the surface plasmon resonance technology to describe the anti-TCZ HAHA isotype, especially aimed at detecting anti-TCZ IgE HAHA which might be associated with hypersensitivity. In addition, this assay was designed to localize the epitope on TCZ against which the anti-TCZ HAHAs are directed.

In addition the following two assays were run on the same samples:
• **Fragment antigen-binding (Fab) Assay** in a bridging ELISA format with high sensitivity to detect all subtypes of anti-TCZ HAHAs that bind to the Fab fragment of TCZ.
• **IgE Assay** based on the commercially available UniCAP® assay system (Pharmacia Diagnostics, Uppsala, Sweden) to measure anti-TCZ HAHAs of the IgE isotype.

These latter two assays, developed by Chugai Pharmaceutical Co. Ltd., were performed by Roche to enable comparisons of results generated in the Roche Phase 3 Clinical program with those of Chugai's clinical development program, for Japanese regulatory authorities.

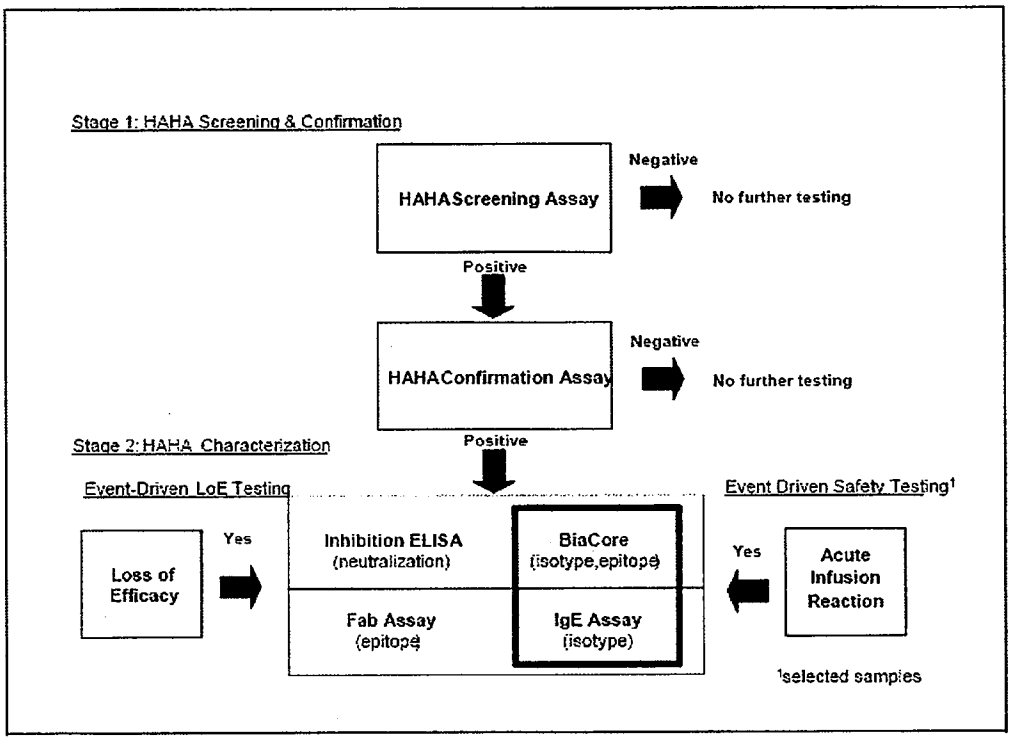


Figure 2.6.2.1. Immungenicity testing strategy.

A brief description of assays for antibody testing is listed below. Refer to Dr. Feldman's review (Product) for review on the technical validation of all of these assays, including information on standardization, reference materials, assay validation, selectivity, specificity, and sensitivity.

Stage 1 screening and confirmation assays:
The anti-tocilizumab antibody screening and confirmation assay consists of a sandwich type ELISA with an additional competitive displacement step for the confirmation assay. The assays include the detection of antibodies directed against the constant region of tocilizumab in the assay system for anti-drug antibodies.

The ELISA utilizes tocilizumab immobilized on microtiter plates for the capture of antitocilizumab antibodies complexed with pre-incubated digoxigenin-labeled tocilizumab

(tocilizumab-DIG). The bound complex of anti-tocilizumab antibody and tocilizumab-DIG is detected by a peroxidase-conjugated anti-DIG antibody reacting with its substrate ABTS and subsequent photometric readout.

The anti-tocilizumab antibody screening assay could also be reactive to auto-antibodies (eg, rheumatoid factor and immature IgMs). In addition, it has been shown that the presence of elevated levels of sIL-6R (2500 ng/mL) can result in a false-positive signal in the screening assay.

During the process of method validation, it was established that the presence of tocilizumab in the test sample produced a progressive inhibition of the signal. Spiking positive-control antibody standards with 3 µg/mL tocilizumab inhibited assay responses up to and including 100 ng-equiv./mL to below the assay cut-point. With 10 µg/mL tocilizumab, assay responses up to and including 300 ng-equiv./mL were inhibited to below the assay cut-point, and with 100 µg/mL tocilizumab, assay responses up to at least 10,000 ng-equiv./mL were inhibited. The C_{min} of TCZ at 8 mg/kg in clinical studies was approximately 10 µg/mL. Therefore, the sensitivity of the method may be reduced by the presence of TCZ in the serum samples. The low immunogenicity rate observed may be partly due to assay insensitivity.

Confirmation of positive screening results (ie, differentiation between nonspecific and specific binding) was performed by means of a displacement reaction step. This essentially uses the same method except that the pre-incubation stage of the assay also includes an inhibitory bulk of unlabeled tocilizumab together with the anti-tocilizumab antibody and tocilizumab-DIG. If the decrease in absorbance due to the presence of tocilizumab was less than 20%, the test result was considered "negative". If the decrease in absorbance was 20% or more, the test result was considered "positive".

This assay was used in studies BP19461, WA17822, WA17823, WA17824, WA18062, WA18063, WA18695 and WA18696.

Table 2.6.2.1 Performance Summary of the Anti-Tocilizumab Antibody Screening and Confirmation Assay.

Validation Site	Assay Range, ng-equiv./mL	Screening Cut-point Sensitivity, ng-equiv./mL	Accuracy, %		Precision, %	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
—	15.6 – 1,000 (HV)	22.4	100.5 to 104	91.8 to 98.5	2.5 to 6.6	4.2 to 6.4
—	15.6 – 1,000 (RA patients)	94.3	n.d.	n.d.	n.d.	n.d.
—	7.81 – 1,000 (HV)	13.0	84.8 to 93.1	91.3 to 92.2	1.8 to 2.0	6.8 to 8.0
—	7.81 – 1,000 (RA patients)	61.4	n.d.	n.d.	n.d.	n.d.

HV: healthy volunteers; n.d.: not done RA: rheumatoid arthritis.

b(4)

Neutralizing Antibody Assay, Inhibition ELISA:

The concentration of neutralizing antibodies to tocilizumab in human serum was determined by an "inhibition ELISA". The inhibition ELISA is a functional assay that is based on its potential to measure anti-tocilizumab antibodies which are capable of inhibiting the binding of tocilizumab to its target antigen, IL-6R. Its primary purpose, therefore, is to detect antibodies with potential tocilizumab-neutralizing activity.

The ELISA method is based on pre-incubating anti-tocilizumab antibody standard, QC samples and/or test samples with a fixed quantity of digoxigenin-labeled tocilizumab (tocilizumab-DIG) before adding the pre-incubation solution to microtiter plates coated with human sIL-6R. Unbound tocilizumab-DIG will bind to immobilized sIL-6R, whereas tocilizumab-DIG complexed with anti-tocilizumab antibodies will not. The amount of tocilizumab-DIG bound to sIL-6R is detected by a peroxidase-conjugated anti-DIG antibody reacting with its substrate ABTS and subsequent photometric readout. In the presence of neutralizing anti-tocilizumab antibodies, the baseline assay signal decreases and concentration equivalents can be interpolated from an anti-tocilizumab calibration curve prepared at the same time. A positive control, rabbit polyclonal antitocilizumab antibody, is used as the analytical standard to construct the calibration curves.

This assay was used in studies WA17822, WA17823, WA17824, WA18062, WA18063, WA18695 and WA18696.

Table 2.6.2.2. Performance Summary of the Inhibition ELISA.

Validation Site	LLOQ, ng-equiv./mL	Assay Range, ng-equiv./mL	Accuracy, %		Precision, %	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
———	211	141 – 2,400	94.4 to 119.6	87.2 to 117.6	1.7 to 7.1	5.1 to 12.9
———	211	211 – 2,400	89.1 to 126.9	74.7 to 103.0	0.5 to 13.2	2.6 to 17.6

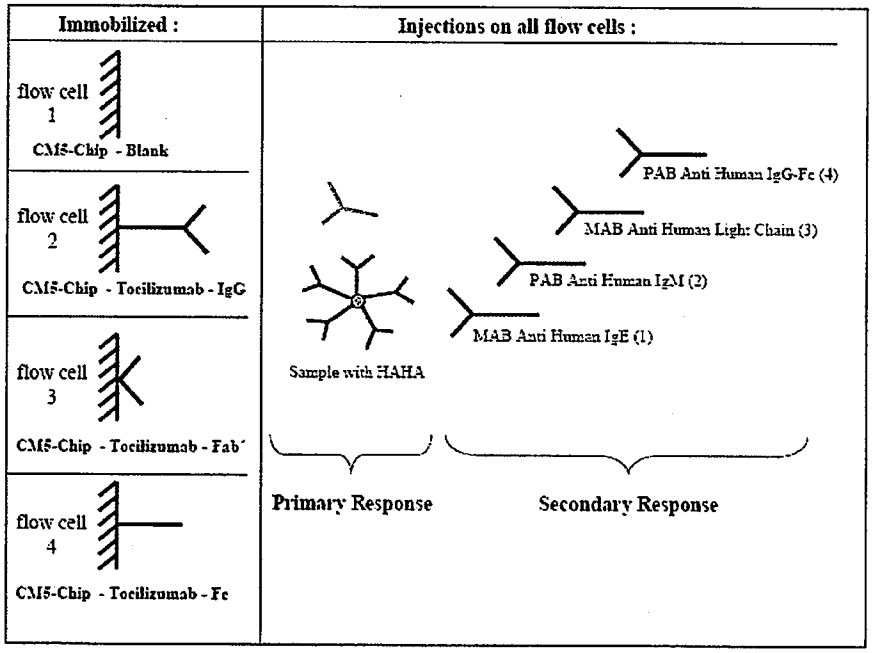
b(4)

Antibody Isotyping Assay, BiaCore Assay

The BiaCore system is based on surface plasmon resonance technology and is used to:

- detect HAHAs
- roughly localize the epitope (Fab or Fc) on tocilizumab to which the HAHAs bind
- determine the isotype of the HAHAs (IgG, IgE or IgM)

Full-length tocilizumab and its Fab and Fc fragments are immobilized in parallel on the BiaCore CM5 chips. For this purpose, all four flow cells of the chip are coated with the streptavidin-derivative neutravidin. Biotinylated, full-length tocilizumab and biotinylated Fab and Fc fragments are each separately injected into one single flow cell, with subsequent immobilization on the surface of each flow cell. The first flow cell is reserved as a reference flow cell.



This assay was used in studies WA17822, WA17823, WA17824, WA18062, WA18063, WA18695 and WA18696.

Anti-Tocilizumab Antibody Assay, Fab Assay

The Fab assay used for the determination of anti-tocilizumab antibodies is a bridging EIA using antibody fragments (Fab) of tocilizumab. This assay is specific for HAHAs directed against the antigen-binding part of tocilizumab. Anti-tocilizumab antibodies are captured by the tocilizumab-Fab and detected by biotinylated tocilizumab-Fab (secondary antibody), avidin-labeled peroxidase (POD) and its substrate *o*-phenylenediamine dihydrochloride (OPD). The Fab assay was validated and the LLOQ set at 3.91 ng/mL using a rabbit polyclonal anti-tocilizumab antibody as a positive standard.

Table 2.6.2.3. Performance Summary of the Fab Assay.

Validation Site	LLOQ, ng/mL	Assay Range, ng/mL	Accuracy, %		Precision, %	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
—	3.91 (HV)	3.91 – 500	98.2 to 100.9	94.2 to 95.8	1.7 to 2.0	5.6 to 11.1
—	3.91 (RA patients)	3.91 – 1,250	70.4 to 71.6	74.7 to 78.9	5.3 to 7.3	5.9 to 9.0

HV: healthy volunteers; RA: rheumatoid arthritis

b(4)

Anti-Tocilizumab Antibody Assay, IgE Assay (UniCAP®)
This assay used for the determination of anti-tocilizumab IgE-antibodies in human serum is based on the commercially available ImmunoCAP® assay system (UniCAP® Specific IgE, UniCAP® 1000, Sweden Diagnostic Inc.). This system uses allergens covalently bound to a cellulose carrier which is contained in a reaction capsule (CAP).

Due to the very limited availability of specific anti-tocilizumab IgE antibody-positive human serum, only a limited assay validation for anti-tocilizumab IgE antibody is available. Assay results are displayed as specific IgE antibody titers (UA/mL). The assay range is from 0.35 to 100 UA/mL. Inter-assay precision is 10.3%

2.6.3 What bioanalytical methods were used to assess the pharmacodynamic effect of the drug?

IL-6
A commercial assay (Quantikine® Human IL-6 Immunoassay, R&D Systems Inc., Catalog Number D6050) was used to measure serum concentrations of endogenous IL-6. This assay uses a monoclonal antibody and polyclonal antibody conjugate in a sandwich ELISA format and provides a quick, sensitive and specific method to quantify human IL-6 levels.

The sensitivity of the IL-6 assay is 3.13 pg/mL. A modified version of the assay which uses an amplification enhancer, thereby achieving a higher sensitivity of 0.156 pg/mL, is also available commercially (Quantikine® HS Human IL-6 Immunoassay, R&D Systems Inc., Catalog Number HS600B).

Assay validation revealed that the measurement of IL-6 is insensitive to the addition of recombinant human sIL-6R. Therefore, it can be assumed that the measurement of IL-6 present in the experimental samples reflects the total concentration of IL-6, ie, the concentration of free IL-6 plus the amount of IL-6 bound to sIL-6R.

Table 2.6.3.1. Performance Summary of the IL-6 Assay.

Validation Site	LLOQ, pg/mL	Assay Range, pg/mL	Accuracy, %		Precision, %	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
	3.13	3.13 – 300	80.9 to 94.3	81.8 to 99.7	0.6 to 3.6	3.9 to 8.3
	3.13	3.13 – 300	88.6 to 96.4	95.6 to 96.2	2.2 to 6.6	4.7 to 8.6
	0.156	0.156 – 10.0	79.4 to 90.5	77.7 to 85.8	2.0 to 5.3	4.9 to 11.5

b(4)

IL-6R

A commercial assay (Quantikine® Human sIL-6R Immunoassay, R&D Systems Inc., Catalog Number DR600) was used to measure serum concentrations of endogenous sIL-6R. This assay uses a monoclonal antibody and polyclonal antibody conjugate in a sandwich ELISA format and provides a quick, sensitive and specific method to quantify human sIL-6R levels.

The sensitivity of the sIL-6R assay is 31.3 pg/mL. Assay validation revealed that the measurement of sIL-6R is insensitive to the addition of recombinant human IL-6 but is sensitive to the presence of tocilizumab. For instance, the recovery of 50 ng/mL sIL-6R in the presence of 500 µg/mL tocilizumab was 74.9% compared to a control without tocilizumab. Therefore, it can be assumed that the measurement of sIL-6R in the experimental samples reflects the total amount of free sIL-6R plus the total amount of sIL-6R complexed with IL-6, plus an uncertain fraction of sIL-6R which has been bound by tocilizumab.

Table 2.6.3.2. Performance Summary of the sIL-6R Assay.

Validation Site	LLOQ, pg/mL	Assay Range, pg/mL	Accuracy, %		Precision, %	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
———	31.3	31.3 – 2,000	94.6 to 106.9	107.8 to 115.2	2.1 to 3.9	5.1 to 8.1
———	31.3	31.3 – 2,000	83.6 to 98.8	97.1 to 109.9	3.0 to 6.2	6.8 to 13.3

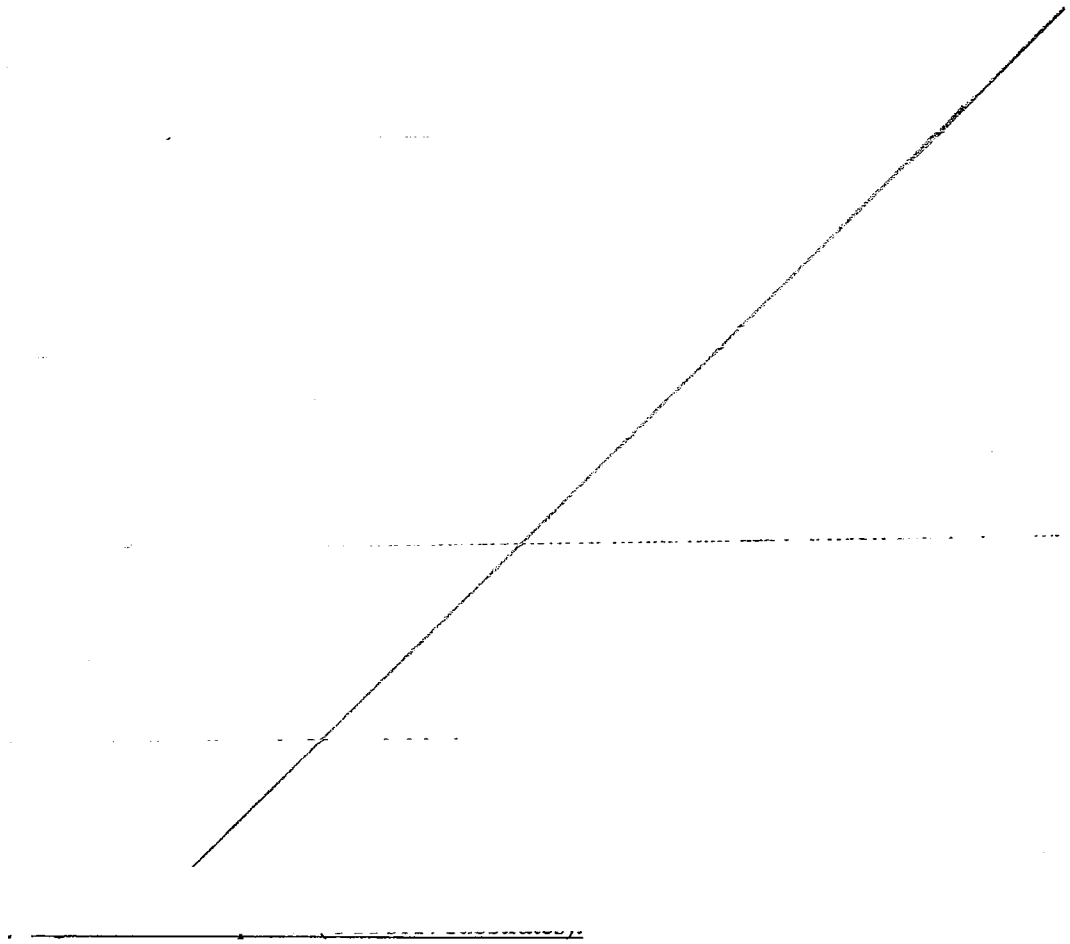
b(4)

To determine the relative amounts of free sIL-6R and sIL-6R complexed with tocilizumab in human serum, a method which combines the separation of free sIL-6R and sIL-6R bound to tocilizumab, with subsequent determination of sIL-6R, was developed. This assay is based on serum fractionation using high-performance liquid chromatography (HPLC) equipped with a gel filtration column. Retention times of the analyte peaks were confirmed with spiked samples and commercial molecular weight markers.

3 Labeling Recommendation

The labeling recommendations that are mostly related to Clinical Pharmacology are shown below with tracked changes. Refer to the approval letter for the full text of the final labeling.

FULL PRESCRIBING INFORMATION



b(4)

18 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 2

4.2 Individual Study Reviews

4.2.1 Study BP19461 Part 1: An evaluation of the safety of supra-therapeutic doses following single doses in healthy subjects

Report no. 1025632 / October 2007. This clinical study report covers Part 1 of the study only

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Study Period:	November 1, 2005 to October 30, 2006
Investigators:	Dr Christopher Kirkpatrick, Dr Adam Foley-Comer
Study Site:	Roche Clinical Pharmacology Unit, Welwyn Garden City, Hertfordshire, England
Sample Analysis Periods:	December 29, 2005 to August 15, 2006 (TCZ) May 8, 2007 to May 14, 2007 (Anti-TCZ antibody)
Analytical Site:	[redacted] b(4)

Study Rationale: Although it is not generally required for a biological product, the Sponsor conducted a thorough QT/QTc study for TCZ (Study 19461, Part 2). The Sponsor conducted this study to provide data to address the precautionary statement in the label approved for TCZ in Japan for the orphan indication of Castleman's disease: "In the clinical studies, cardiac abnormalities were observed and therefore, electrocardiography should be conducted periodically with a caution for the changes during the treatment with ACTEMRA™".

The present study was designed to formally assess whether administration of tocilizumab under controlled conditions affects cardiac electrophysiological parameters according to the ICH E14 guideline. In order to fulfill this regulatory requirement, this study was carried out in two parts. Part 1 was a single ascending dose study to establish safety and tolerability of tocilizumab and identify a high dose suitable to be used in part 2. Part 2 was a thorough QT study, designed to evaluate the QT/QTc interval prolongation and proarrhythmic potential of tocilizumab.

Study report for Part 1 is reviewed here and Part 2 of the study is on-going at the time of BLA submission. The final study report was submitted in July 2008 and will be reviewed by QT-IRT.

OBJECTIVES	The primary objective was: • to investigate the safety and tolerability of tocilizumab at supra-therapeutic doses in healthy subjects in order to support the dose selection for part 2 of the study (thorough QT study) The secondary objective was: • to investigate the pharmacokinetics (PK) of tocilizumab at supra-therapeutic doses in healthy subjects
STUDY DESIGN	This was a single center, randomized, double-blind, placebo-controlled, parallel group study.
NUMBER OF SUBJECTS	38 subjects planned: 4 dose groups with 8 subjects each (6 on active drug and 2 on placebo) with an additional safety group of 6 subjects for the highest safe and well-tolerated dose; 51 subjects randomized; 36 subjects dosed.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Healthy male or female volunteers, aged between 18 and 65 years, inclusive.
TRIAL DRUG / STROKE (BATCH) No.	Tocilizumab / batch no. MR5C06.
DOSE / ROUTE / REGIMEN / DURATION	Tocilizumab doses of 2, 10, 20 and 28 mg/kg administered as an intravenous infusion over a 1 hour period with an infusion speed of 20 mL/hour for 15 minutes, increased to 260 mL/hour for 45 minutes.
REFERENCE DRUG / STROKE (BATCH) No.	Matching placebo / batch no. MR4J01.
DOSE / ROUTE / REGIMEN / DURATION	Placebo intravenous infusion over a 1 hour period with an infusion speed of 20 mL/hour for 15 minutes, increased to 260 mL/hour for 45 minutes.
CRITERIA FOR EVALUATION	
PHARMACOKINETICS:	Serum concentrations of tocilizumab were measured and the following parameters were evaluated: C_{max}, C_{last}, t_{max}, AUC_{last}, AUC_{inf}, k_{el}, $t_{1/2}$, CL, V_z, V_{ss} and MRT_{inf}.
SAFETY:	Adverse events (AEs), laboratory safety tests, vital signs, electrocardiograms (ECGs) and anti-tocilizumab antibodies.

Sample Collection: Blood samples for PK analyses were collected at the following time points: predose, 1, 2, 4, 8, 12, 24, 48, 96, 168, 240, 336, 504 and 672 hours post the start of infusion of tocilizumab.

Sampling for anti-tocilizumab antibodies was carried out on day 29 and at the follow-up visit.

Sample Analysis: Serum concentrations of tocilizumab were measured using a validated enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification of this assay was 0.1 µg/mL. This assay was carried out at the [redacted] The inter-assay precision (CV%), as determined from the analysis of QC samples ranged from 9.5% to 12.1%. There was no marked inaccuracy in the results from these QC samples (mean accuracy 92.0% [n = 38] to 95.6% [n = 38]). b(4)

The detection of anti-tocilizumab antibodies in serum was initially carried out in all samples from subjects receiving active drug using a validated semi-quantitative bridging ELISA (screening assay). For serum samples that were found positive in the screening assay, the

presence of specific anti-tocilizumab antibodies was confirmed or excluded using the same ELISA method but with an appropriate immunodepletion step (ie, addition of bulk tocilizumab, confirmation assay). Samples were then confirmed as containing specific anti-tocilizumab antibodies if the mean assay response in the confirmation sample was less than 80% of the control sample. The lower limit of quantification of the screening and confirmation assay was 7.81 ng-equivalent/mL. The anti-tocilizumab antibody results were reported as positive or negative. This assay was carried out at the [b(4)

]

Subjects: Of the total 51 subjects randomized, 15 subjects withdrew from the study before receiving study medication and 36 received a single dose of study drug as planned (26 received tocilizumab and 10 received placebo). All 26 subjects who received tocilizumab were eligible for the PK evaluation. Of the 36 subjects dosed, 17 were male and 19 female (Table 1). Mean age varied from 26 to 40 years with an age range of 18 to 61 years across groups. The majority of subjects were White and of non-Hispanic origin.

Table 1. Disposition of Subjects.

Dose Group	Dose (mg/kg)	Subjects Randomized			Subjects Dosed		
		Total	Tocilizumab	Placebo	Total	Tocilizumab	Placebo
1	2	8	6	2	7	5	2
2	10	11	8	3	8	6	2
3	20	16	12	4	7	5	2
4	20	8	6	2	7	5	2
5	28	8	6	2	7	5	2
	Total	**51**	**38**	**13**	**36**	**26**	**10**

In the 10 mg/kg dose group, the infusion rate was incorrectly set to 0.5 mL/h rather than 20 mL/h at the start of infusion for subjects 1011, 012 and 013 receiving tocilizumab and for subject 014 receiving placebo. Once the error was detected, the infusion rates were set to the correct values (20 mL/h for 15 min followed by 260 mL/h for the remainder of the infusion, ie, approximately 45 minutes). Because the incorrect infusion rate at the beginning of the infusion was very small, ie, 0.5 mL/h, the amount of tocilizumab entering the body was negligible (< 0.2% of the total dose). With exception of a small time shift (t_{lag}) in the concentration-time profile, the resulting concentration-time profiles were comparable to those where the infusion was given as per protocol.

Results:

Pharmacokinetics:

The arithmetic mean serum concentration-time profiles for tocilizumab following administration of single iv doses of 2, 10, 20 and 28 mg/kg are shown in Figure 1. Serum concentrations of tocilizumab decreased with time in a biphasic manner.

Mean PK parameters (with CV%) for each dose of tocilizumab are listed in Table 2. Tocilizumab showed a dose-related increase in systemic exposure (AUC, C_{max}). With increasing doses (from 2 to 28 mg/kg), the increase in C_{max} was approximately dose proportional (Figure 2, p-value for the deviation from dose proportionality of 0.168), whereas the increase in AUC was

more than dose proportional (Figure 3, p-value for the deviation from dose proportionality of <0.0001). The over-proportional increase in AUC with increasing dose seemed more pronounced between the 2 and 10 mg/kg doses than between the higher doses (10, 20 and 28 mg/kg).

Inter-subject variability across all dose groups (expressed as CV%) ranged from 11% to 24% for AUC_{inf} and from 8% to 20% for C_{max} (Table 2).

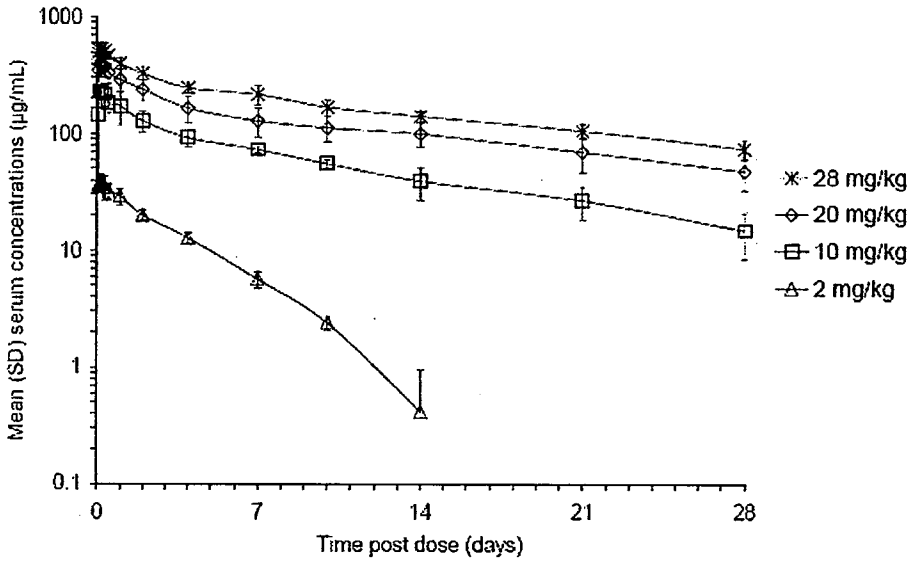

Figure 1. Arithmetic Mean (± SD) Serum Concentration-Time Profiles of Tocilizumab by Dose Group.

Table 2. Summary of Mean[1] (CV%) Pharmacokinetic Parameters of Tocilizumab in Serum by Dose Group.

Parameter	2 mg/kg N = 5	10 mg/kg N = 6	20 mg/kg N = 10	28 mg/kg N = 5
Cmax (µg/mL)	41.9 (8%)	242 (13%)	410 (20%)	558 (14%)
tmax[2] (h)	4 (1-8)	4 (2-8)	3 (1-8)	4 (1-4)
AUCinf (h*µg/mL)	3310 (11%)	42300 (19%)	97300 (24%)	147000 (12%)
AUClast (h*µg/mL)	3210 (13%)	37800 (16%)	77800 (22%)	115000 (9%)
t1/2 (h)	54.0 (20%)	201 (15%)	277 (13%)	293 (16%)

MRTinf (h)	82.1 (7%)	282 (18%)	401 (14%)	428 (17%)
Vss (mL/kg)	50.0 (13%)	67.5 (14%)	85.7 (24%)	81.4 (14%)
Vz (mL/kg)	47.4 (23%)	69.5 (12%)	85.3 (21%)	80.5 (13%)
CL (mL/h/kg)	0.609 (10%)	0.243 (17%)	0.217 (24%)	0.192 (11%)

1 Values reported as arithmetic means.
2 Median values (min-max) reported for t_{max}.

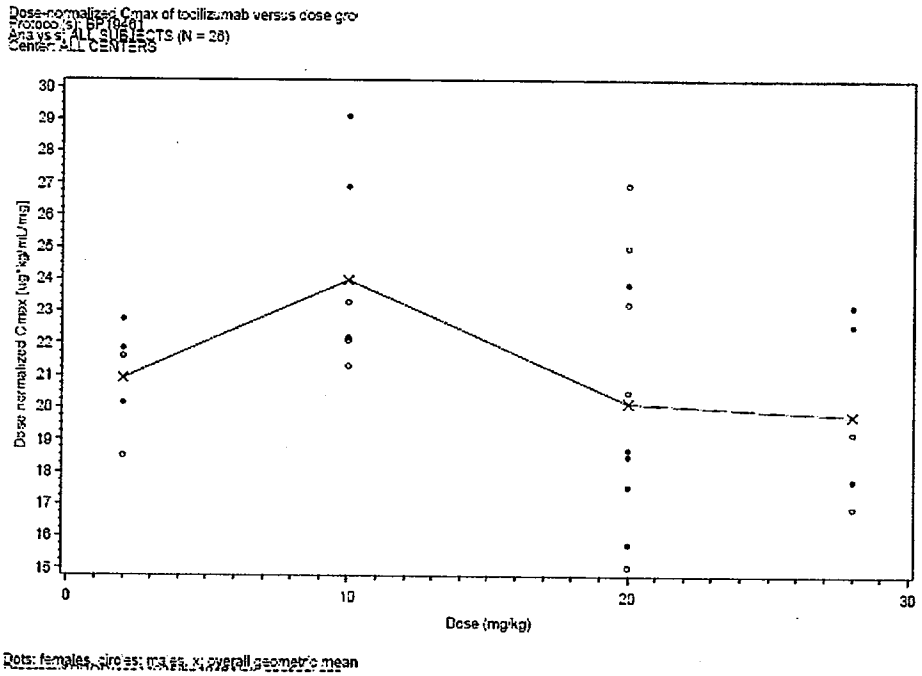

Figure 2. Dose-Normalized Cmax for Tocilizumab versus Dose.

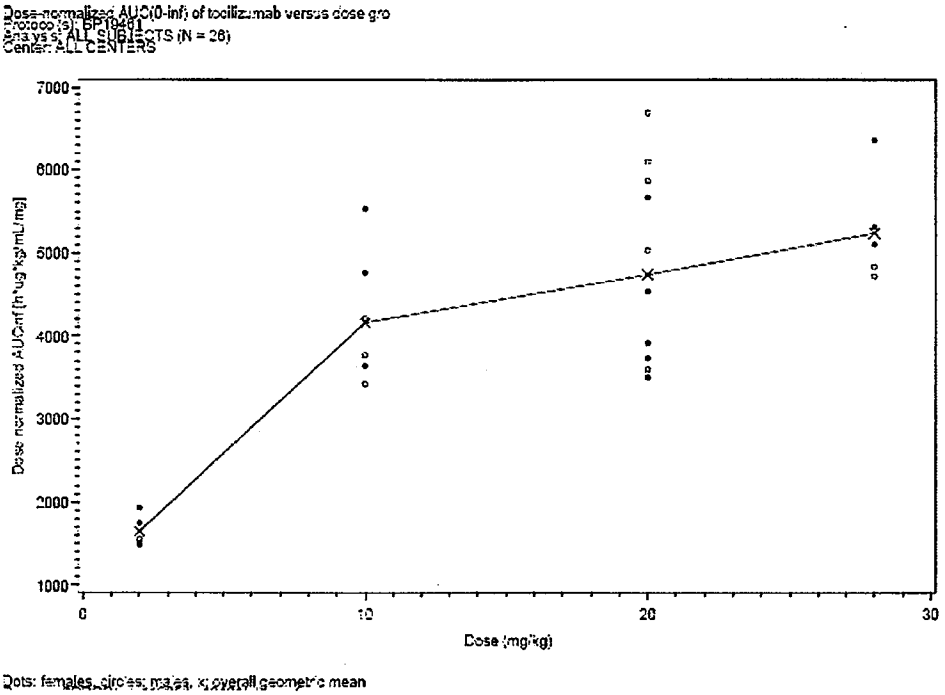

Figure 3. Dose-Normalized AUC_{inf} for Tocilizumab versus Dose.

Immunogenicity:

Two out of five subjects who received 2 mg/kg (subjects 04 and 08) had positive results for anti-tocilizumab antibodies (in the screening and confirmation assay). Subject 04 had a positive result on days 29 and 50 and subject 08 on day 50. The PK for these two subjects was comparable to that of the other subjects who received 2 mg/kg (see table below). Subjects who received 10, 20 or 28 mg/kg did not test positive for anti-tocilizumab antibodies. As of note, no blood samples were collected for anti-tocilizumab antibody testing before drug administration (ie, at baseline), false positives cannot be distinguished from true positives.

Individual Pharmacokinetic Parameters (Including Summary Statistics) by Dose Group

MTDOSE (mg/kg)	PT	SEX	Cmax (ug/mL)	Tmax hr)	AUClast (hr*ug/mL)	AUCINF_obs (hr*ug/mL)	MRTINF_obs (hr)	t1/2 (hr)	Vz_obs (mL/kg)	Cl_obs (mL/hr/kg)	Vss_obs (mL/kg)
2	1	MALE	37.0	1.02	3110	3120	80.7	43.5	40.2	0.642	51.8
	4	MALE	43.2	2.17	2880	3100	88.2	64.2	59.7	0.645	57.0
	5	FEMALE	45.5	4.02	3770	3870	86.3	63.0	47.0	0.517	44.6
	6	FEMALE	40.3	4.00	2810	2980	81.7	58.1	56.3	0.672	54.9
	8	FEMALE	43.7	8.00	3490	3500	73.3	41.1	33.9	0.572	41.9
		N	5	5	5	5	5	5	5	5	5
		Mean	41.9	3.84	3210	3310	82.1	54.0	47.4	0.609	50.0
		SD	3.33	2.65	410	367	5.79	10.9	10.8	0.0635	6.51
		Min	37.0	1.02	2810	2980	73.3	41.1	33.9	0.517	41.9
		Median	43.2	4.00	3110	3120	81.7	58.1	47.0	0.642	51.8
		Max	45.5	8.00	3770	3870	88.2	64.2	59.7	0.672	57.0
		CV%	7.95	69.1	12.8	11.1	7.05	20.3	22.7	10.4	13.0
		G. Mean	41.8	3.09	3190	3300	81.9	53.0	46.4	0.607	49.7
		CV% G. Mean	8.15	90.7	12.6	10.8	7.20	21.4	23.8	10.8	13.3

Conclusions:
Human PK studies showed that clearance (CL) of tocilizumab was concentration-dependent. CL decreased with increased dose. Mean CL was estimated as 0.609 mL/h/kg for the 2 mg/kg dose and decreased with increasing doses to 0.192 mL/h/kg for the highest dose of 28 mg/kg. The proposed clinical dose is 8 mg/kg every 4 weeks. 8 mg/kg was not studied in this study and 10 mg/kg was a dose close to 8 mg/kg. Mean apparent $T_{1/2}$ at 10 mg/kg was 201 hours (8 days). Mean V_z at 10 mg/kg was 70 mL/kg. The highest systemic exposures to tocilizumab were achieved with the 28 mg/kg dose, with mean AUCinf and Cmax values of 147000 h*µg/mL and 558 µg/mL, respectively.

The concentration-dependent clearance is likely a sum of two clearance mechanisms: the nonspecific linear clearance by the reticuloendothelial system and the antigen-mediated (e.g., IL-6R) saturable clearance.

Dose Selection for Part 2 (thorough QT):
Although the safety profile was comparable between 28 mg/kg dose and 20 mg/kg dose, the Sponsor selected 20 mg/kg dose for the thorough QT study (part 2 of study BP19461). The main reasoning for this was based on the finding that time to recovery to normal levels of neutrophils was dose related. Although marked decreases in neutrophils have, thus far, not been associated with any apparent increased frequency or severity of infections, the known mechanisms of IL-6 receptor blockade with tocilizumab might have an immunosuppressive effect on healthy subjects. It was thought that administering doses that were higher than 20 mg/kg (28 mg/kg or higher) in a large group of healthy subjects (ie, 30, as planned for each treatment group in the thorough QT part of this study) would place healthy subjects at an unnecessary and potential risk of serious infections. In addition, because systemic exposure to tocilizumab is expected to increase further with increasing doses, this would impact the subjects' immune systems over a longer period of time.

4.2.2 Study LRO300: A double-blind, randomized, placebo-controlled study of the safety, tolerance, pharmacokinetics and efficacy of escalating single intravenous doses of MRA in patients with rheumatoid arthritis

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Study Period: July 2, 1998 to December 13, 2000
Investigator: [redacted] b(4)
Study Sites: 6 centers in UK

Objectives:

- To evaluate the safety and tolerance of a range of single i.v. doses of MRA in patients with RA.
- To evaluate the antigenicity of single i.v. doses of MRA in patients with RA.
- To evaluate the pharmacokinetics of single i.v. doses of MRA in patients with RA.
- To assess the potential efficacy of single i.v. doses of MRA in patients with RA.

Study Design:
This was a double-blind, randomized, placebo-controlled clinical study of the safety, tolerance, antigenicity, pharmacokinetics and efficacy of single i.v. infusion of MRA in four cohorts of escalating doses in patients with RA with a follow-up period of assessments until Week 8. Four sequential cohorts of 12 patients were to be enrolled. Each cohort was assigned one of the following dose levels 0.1, 1.0, 5.0 or 10.0 mg/kg. Nine patients were to receive the active drug and three placebo.

Diagnosis and Criteria for Inclusion : Patients aged 18-75 years that were not of child bearing potential. Patients with RA according to the American College of Rheumatology (ACR) criteria and active disease who had failed at least one disease modifying rheumatic drug (DMARD)/cytotoxic drug treatment. Patients were excluded on the basis of specified concurrent disorders or prohibited concomitant medications.
Investigational Product, Dose, Mode of Administration, Batch No. : MRA (a humanised anti-human interleukin –6 [IL-6] receptor monoclonal antibody) given by i.v. infusion at doses of 0.1, 1.0, 5.0 or 10.0 mg/kg. Batch number: R7F03.
Duration of Treatment : Single dose infused over 1 hour.
Reference Therapy, Dose, Mode of Administration, Batch No. : Placebo (sterile saline) given by i.v. infusion over 1 hour in matched infusions. Batch number not applicable.

Sample Collection: Blood and urine samples for PK analyses were collected at the following time points: predose, 1 (blood only), 4, 8 (blood only), 24, Days 2, 7, 14, 21, 28, 42 and 56 (Weeks 1, 2, 3, 4, 6 and 8) post the start of infusion of tocilizumab.

Blood samples for the measurement of serum anti-MRA antibodies were taken at Day 1 (prior to start of infusion) and at Days 7, 14, 21, 28, 42 and 56.

Sample Analysis: Pharmacokinetic analyses of MRA in serum and urine and MRA antibodies were performed by [redacted] The analysis of serum anti-MRA antibody was performed using an immunoassay procedure previously established and validated by [redacted] (Report number CGI044/983189). The lower limit of quantification was set at 3.9 b(4)

ng/ml. Test samples that were found to have detectable levels of activity were reanalysed following preabsorption with excess MRA to determine the specificity of the binding.

Subjects:
All 45 patients who entered the clinical study and received treatment were used for all safety and efficacy reporting. The mean age of the Total Population was 58.2 years (range 35.1 to 76.0 years). The overall mean height in the Total Population was 165.6 cm (range 151 to 191 cm) and the mean weight was 71.1 kg (range 50-100 kg). The majority of the patients (33; 73.3%) were Caucasian. In addition, five patients were Asian (11.1%) and seven were Negroid (15.6%). Overall, the majority of patients were female (30; 66.7%). In the MRA treatment groups there were between 66.7 and 77.8% females. However, in the placebo group there were more male patients (54.5%).

The median duration of RA in the Total Population was 8.3 years (range 0.3 to 45.3 years). All patients had previously received between one and six different DMARD/cytotoxic therapies.

Table 1. Patient Demographics.

Variable	Treatment Group				
	Placebo	MRA			
		0.1 mg/kg	1.0 mg/kg	5.0 mg/kg	10.0 mg/kg
Total Number of Patients	11	9	9	9	7
Age (years)					
mean±SD	61.8±10.6	54.6±10.0	55.7±9.0	57.2±12.1	61.5±7.8
range	42.5-76.0	36.4-67.2	44.2-70.4	35.1-74.3	48.0-70.6
Height (cm)					
mean±SD	168.9±9.5	161.8±7.9	166.7±11.8	164.7±6.9	165.4±6.0
range	155-182	151-177	152-191	155-180	157-174
Weight (kg)					
mean±SD	73.3±12.6	64.6±12.2	72.9±15.4	74.9±13.6	68.6±7.7
range	54.0-90.1	50.0-86.0	52.0-100.0	62.0-99.0	57.0-78.0
Gender					
Male (n, %)	6, 54.5	3, 33.3	2, 22.2	2, 22.2	2, 28.6
Female (n, %)	5, 45.5	6, 66.7	7, 77.8	7, 77.8	5, 71.4
Race					
Caucasian (n, %)	9, 81.8	7, 77.8	5, 55.6	6, 66.7	6, 85.7
Asian (n, %)	1, 9.1	2, 22.2	1, 11.1	-	1, 14.3
Negroid (n, %)	1, 9.1	-	3, 33.3	3, 33.3	-

Source data: End-of-Text Table 2.1, Table 2.2 and Table 11.6, Section 14.1; Listings 3 and 7 (Appendix 16.2.4).

Mean CRP levels, ESR and sIL-6R levels were similar at baseline between the treatment groups, whereas mean IL-6 levels were much more variable between groups (range 3.2 to 923.6 ng/ml).

Results:
Pharmacokinetics:
The mean pharmacokinetic parameters of MRA in patients with RA following single 1 hour i.v. infusions of MRA are presented in Table 2 with standard deviations in parentheses.

Table 2. Mean (±SD) Pharmacokinetic Parameters of MRA in Patients with RA Following a Single 1 hour Infusion of MRA.

Pharmacokinetic Parameter	MRA			
	0.1 mg/kg	1.0 mg/kg	5.0 mg/kg	10.0 mg/kg
C_{max} (µg/ml)	1.96 (1.26)	17.9 (4.7)	123 (21)	273 (121)
T_{max} (hours)	1.192	4.000	1.183	4.250
AUC_t (µg/hour/ml)	18 (13)	1177 (839)	18093 (3531)	43560 (17032)
AUC (µg/hour/ml)	- (-)	1608 (-)	19504 (3062)	46099 (18249)
$t_{½}$ (hours)	-	52.9	135.9	158.0
CL (ml/hour/kg)	- (-)	0.74 (-)	0.26 (0.04)	0.26 (0.13)
V_z (ml/kg)	- (-)	54.7 (-)	51.4 (6.2)	56.9 (13.6)
MRT (hours)	- (-)	70.5 (-)	193.2 (39.9)	242.7 (53.1)
V_{ss} (ml/kg)	- (-)	49.7 (-)	49.7 (7.5)	58.7 (22.4)

The rate (Cmax) of systemic availability of MRA to patients increased approximately proportionately with increasing dose from 0.1 to 10.0 mg/kg. The extent (AUCt) of systemic availability of MRA to patients increased by more than the proportionate dose increment from 0.1 to 10.0 mg/kg, following single 1 hour i.v. infusions. At the highest dose level (10.0 mg/kg), the AUCt values of MRA in patients with RA were approximately 24-fold higher than those values predicted from a linear relationship. MRA t½ increased with increasing dose from 1.0 to 10.0 mg/kg. The CL of MRA appeared to decrease with doses of 5.0 mg/kg and higher. The mean Vz of MRA ranged from 51.4 to 56.9 ml/kg and appeared to be independent of the dose of MRA administered.

Urine concentrations of MRA were below the limit of quantification (<12 ng/ml) at all the time points in all patients in the 0.1 mg/kg MRA group and all but one patient in the placebo group (Patient 39: 13.62 ng/ml at Week 1). MRA was not consistently detected in urine in the other treatment groups and ranged from 12.32 to 91.96 ng/ml at 24 hours to 6 weeks post-infusion, reflecting the limited clearance of MRA via kidney elimination.

Immunogenicity:
Anti-MRA antibodies could not be detected in 38 out of 45 patients. Samples from seven patients had measurable assay response above the lower limit of quantification. One patient each in Cohorts 1 and 4, 2 patients in Cohort 2 and three patients in Cohort 3. Six of these seven patients had positive responses at baseline. No significant inhibition of assay response for any of the seven samples was found following preabsorption with MRA. This indicates that the activity was due to non-specific binding.

Conclusions:
Clearance is concentration-dependent. PK parameters in RA patients are similar to those obtained in healthy subjects. The proposed clinical dose is 8 mg/kg every 4 weeks. 8 mg/kg was not studied in this study and 10 mg/kg was a dose close to 8 mg/kg. Mean apparent $T_{1/2}$ at 10 mg/kg was 158 hours (7 days). Mean Vz at 10 mg/kg was 57 mL/kg.

4.2.3. Study MRA221JP: Clinical Pharmacology Study of MRA in Rheumatoid Arthritis Patients with Renal Impairment

Study Period: January 13, 2005 to October 6, 2005
Investigators: [redacted] b(4)
Study Site: [redacted]

Analytical Site: [redacted]

Objective: To investigate the pharmacokinetics of MRA after single administration in rheumatoid arthritis patients with renal impairment, and to evaluate safety as well.

Methodology: The pharmacokinetics of MRA were investigated after single intravenous infusion of the drug at a dose of 8 mg/kg in rheumatoid arthritis patients with renal impairment in an open-label study, and safety was also evaluated. Patients were followed up for 35 ± 2 days after initial dose.

Subjects: Fourteen patients were enrolled in the study, and all received the investigational product once by intravenous infusion and completed tests. Using the creatinine clearance (CrCL) values determined from the mean of 2 lots of 24-hour urine collected during hospitalization after enrolment [Day −1 to Day 0 and Day 0 to Day 1], patients were included as defined below.

Renal impairment classification	CrCL (mL/min)	Target sample size	Enrolled patients	Safety evaluation set Pharmacokinetic analysis set FAS	PPS
Mild	80≥ CrCL >50	≥4	4	4	3
Moderate	50≥ CrCL >30	≥4	5	5	5
Severe	30≥ CrCL >10	No limit	3	3	3
(No renal impairment)	CrCL >80	Excluded as subjects	2	2	0
Total	–	10	14	14	11

The degree of renal impairment was mild in 4 patients, moderate in 5 patients and severe in 3 patients (Table 1). Two patients did not have renal impairment whose CrCL measured at enrolment was ≤80 mL/min, which met the inclusion criteria, but the mean of the two CrCL measurements after enrolment was >80 mL/min (patients without renal impairment). The age (mean ± SD) of the patients was 66.5 ± 6.1 years for the patients with mild renal impairment, 63.2 ± 5.4 years for the patients with moderate renal impairment, 64.0 ± 3.6 years for the patients with severe renal impairment and 63.5 ± 2.1 years for the patients without renal impairment. The disease duration was 14.68 ± 9.72 years for the patients with mild renal impairment, 18.78 ± 5.88 years for the patients with moderate renal impairment, 34.33 ± 10.53 years for the patients with severe renal impairment and 8.57 ± 8.89 years for the patients without renal impairment.

Table 1. Patient Baseline Characteristics.

Patient No	Sex	Age	Body	Height	BMI	SCR	24-hr urine CrCL			Renal impairment classification
							1st (mL/min)	2nd (mL/min)	Mean (mL/min)	
102001	Female	67	43.5	150.5	19.21	05			50.37	Mild
102002	Female	68	52.0	140.4	26.38	0.9			45.94	Moderate
102003	Male	66	60.0	162.3	22.78	1.2			38.82	Moderate
102004	Female	67	43.5	139	22.51	1.2			26.26	Severe
102005	Female	65	66.6	153	28.45	1.1			29.90	Severe
102006	Female	59	53.0	154.4	22.23	0.9			55.25	Mild
102007	Female	60	51.8	151.0	22.72	2.2			20.11	Severe
103001	Female	66	51.1	154.5	21.41	0.7			74.11	Mild
103002	Male	59	55.0	160	21.48	1.64			39.96	Moderate
103003	Female	62	50.0	148	22.83	0.59			88.82	Not impaired
103004	Female	74	50.0	141	25.15	0.53			62.61	Mild
103005	Female	67	50.0	154	21.08	1.52			30.05	Moderate
103006	Female	65	48.6	144.5	23.28	0.6			84.26	Not impaired
103007	Male	56	74.0	172	25.01	1.66			38.59	Moderate

Not impaired = Without renal impairment: CrCL >80 mL/min

b(4)

Investigational product: MRA (Tocilizumab [recombinant]), Lot No.: MR4C05A

Dose and method of administration: 8 mg/kg MRA was intravenously drip infused over 1 hour.

Study Rationale: The kidneys do not appear to be involved in excretion of MRA because MRA was not detected in the urine after administration at a dose of 2 mg/kg in healthy adults. However, because MRA is humanized IgG, elimination of MRA from the body is presumably due in large part to metabolism in the reticuloendothelial systems of the liver, kidneys and spleen. Based on this, it was concluded that it would be preferable to investigate the effect of renal function on the pharmacokinetics of MRA and, as a result, the present study of patients with reduced renal function was conducted.

Sample Collection: Serum samples for TCZ concentration determination were collected at before infusion, and 1, 4, 8 and 24 hours after completing infusion of MRA; on Days 7, 14, 21, 28; and 35 and at withdrawal.

Samples for anti-MRA antibodies were collected at Day 0, Day 35 and withdrawal.

Results:

Pharmacokinetics:

The serum MRA concentration slowly decreased after treatment and followed a similar time course for all of the renal impairment classes (Figure 1).

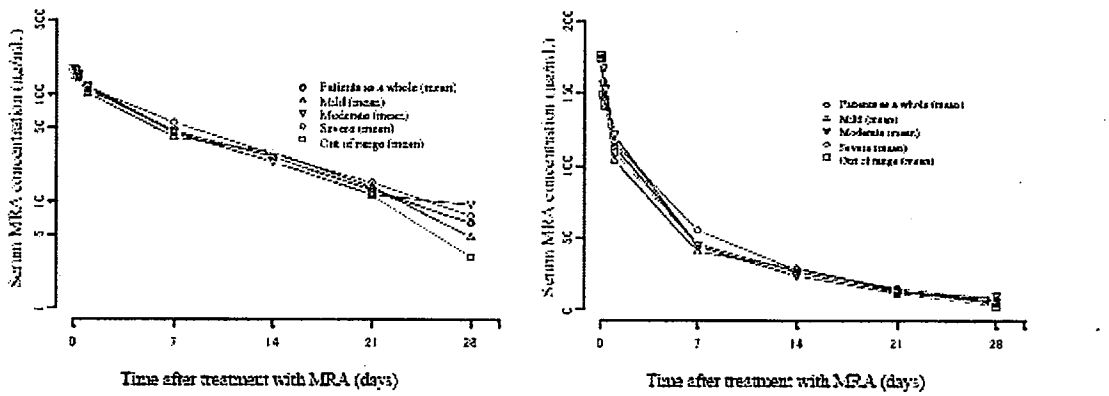

Figure 1. Time course of serum MRA concentration for each renal impairment class (mean ± SD) (Left: log-linear scale; Right: linear scale).

Table 2. List of Pharmacokinetic Parameters by Patient.

		AUCinf hr*ug/mL	AUClast hr*ug/mL	CL mL/hr/kg	Cmax ug/mL	t1/2 hr	kel 1/hr	MRT hr	Vdss mL/kg	Vd mL/kg
Mild renal impairment	102001	7930.49	7421.32	1.01	143.00	48.77	0.0142	69.56	70.17	70.97
	102006	28317.71	27401.23	0.28	181.00	134.87	0.0051	198.75	56.15	54.97
	103001	21607.27	21441.95	0.37	161.00	97.11	0.0071	205.95	76.62	51.87
	103004	27925.03	26999.01	0.28	211.00	124.16	0.0056	205.42	59.13	51.32
Moderate renal impairment	102002	17991.52	17720.95	0.44	191.00	87.23	0.0079	131.01	58.26	55.96
	102003	27016.17	26503.23	0.30	158.00	150.22	0.0046	232.89	68.96	64.18
	103002	17134.58	16517.49	0.47	162.00	99.01	0.0070	145.98	68.62	66.69
	103005	37269.14	35205.10	0.21	172.00	213.22	0.0033	275.22	59.08	66.03
	103007	28457.79	27335.16	0.27	202.00	156.87	0.0042	212.52	57.71	65.38
Severe renal impairment	102004	20349.46	18970.55	0.39	143.00	137.92	0.0050	195.18	76.73	78.22
	102005	39565.15	39068.99	0.20	211.00	141.53	0.0049	216.34	43.74	41.29
	102007	28652.90	28146.64	0.27	163.00	154.68	0.0042	243.46	65.68	64.10
No renal impairment	103003	21148.12	20962.44	0.38	158.00	108.16	0.0064	175.35	66.71	59.03
	103006	26810.27	25873.04	0.30	194.00	129.67	0.0053	205.82	61.41	55.82

Patient No. 102001 (mild renal impairment), who had a lower serum MRA concentration than the other patients throughout the measurement period, had nephritic syndrome, low baseline total protein (3.9 g/dL) and low baseline IgG (524 mg/dL) and a urinary protein of 4+. It is presumed that the serum MRA concentration was low in this patient due to leakage of globulins into the urine.

The effect of renal function on the pharmacokinetics of MRA was compared between the groups using the Cmax and AUClast as indicators, based on the fact that the pharmacokinetics of MRA are non-linear. The Cmax did not differ as a result of the degree of renal impairment, but the AUClast was slightly greater in the patients with severe renal impairment than in the patients of the other renal impairment classes (Table 2).

No correlation between CLcr and Cmax or AUC could be identified (Figures 2 and 3). Examination of the relationship between baseline CrCL and the Cmax and AUClast showed that

the correlation coefficient for CrCL and the Cmax was r=0.08 (regression line: y = 0.09x + 170.73) and the correlation coefficient for CrCL and the AUCfin was r= −0.25 (regression line: y = −93.26x + 28,868.39). The coefficient of correlation with CrCL was therefore small for both parameters.

Table 2. Mean Cmax and AUC based on Renal Fuction.

	Cmax (μg/mL)	AUClast (μg·hr/mL)
Mild (N=4)	174.00 ± 29.14	20,816.00 ± 9334.36
Moderate (N=5)	177.00 ± 18.92	24,796.19 ± 7710.26
Severe (N=3)	172.33 ± 34.95	28,728.73 ± 10,061.85
Normal (N=2)	176.00 ± 25.46	23,417.74 ± 3,472.32

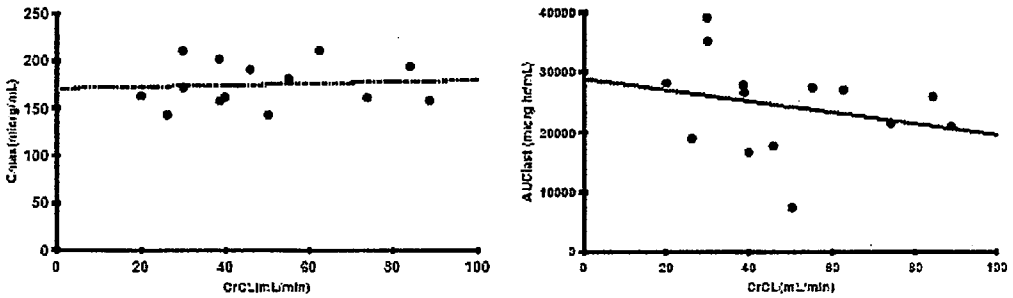

Figure 2. Scatter diagrams for CrCL and Cmax and CrCL and AUClast.

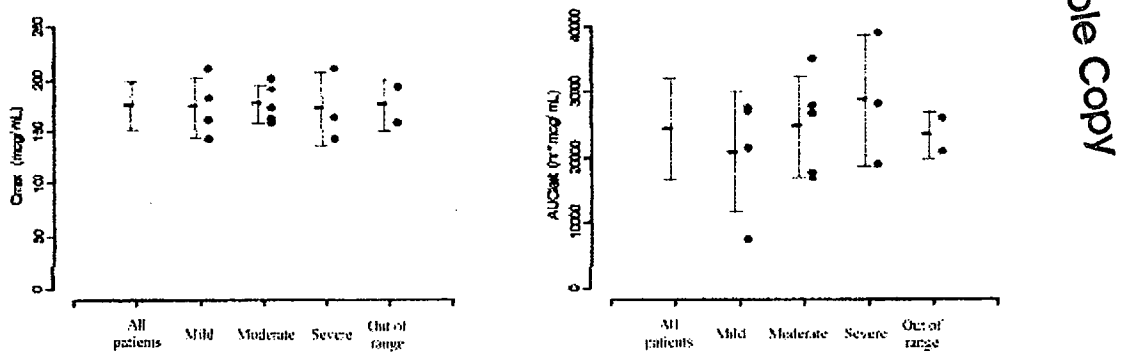

Figure 3. Cmax and AUClast for each renal impairment class.

Immunogenicity:
None of the patients became positive for neutralizing antibodies or IgE antibodies.

Conclusions:
Cmax and AUC were similar in RA patients with various degree of renal impairment. The degree of renal impairment did not appear to affect the pharmacokinetics of MRA. Based on these results, the dosage of MRA does not need to be adjusted for RA patients with renal impairment.

4.2.4 In Vitro Study Report–Study ADM03-0155: Effect of MRA and IL-6 on the expression of drug metabolizing enzyme in human liver

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Rationale of the study: IL-6 is known to suppress the expression levels of the mRNAs that code for drug metabolizing enzymes (cytochrome P450 enzymes [CYPs]). Furthermore, IL-6 is thought to decrease CYP expression levels by promoting hemoxygenase activity. Rheumatoid arthritis patients may have lower CYP expression levels than healthy persons because their serum IL-6 concentrations are higher. When the function of IL-6 is inhibited in such patients by the administration of MRA, CYP expression levels may rise above predosing levels and the serum concentrations of coadministered drugs that are metabolized by CYPs may decrease. On the other hand, repeated administration of MRA is known to increase the serum IL-6 concentration in rheumatoid arthritis patients. This increase in the serum IL-6 concentration is not thought to be a major problem when the serum MRA concentration is maintained because MRA inhibits the effects of IL-6. However, if, for example, MRA is withdrawn and it disappears from the serum, IL-6 signaling will resume, the increased serum IL-6 concentration will decrease the CYP expression levels. The effect will be clinically relevant for drugs with narrow therapeutic index. This preliminary investigation of the effect of IL-6 and MRA on CYP expression levels in human hepatocytes was conducted to guide in vivo drug interaction study design.

Methods: The effects of MRA, IL-6, and sIL-6R on hepatic drug metabolizing enzyme expression levels were investigated by measuring the expression levels of the following mRNAs: the mRNAs that code for the hepatic drug metabolizing enzymes CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, and CYP2E1; the mRNAs that code for HMOX1 and HMOX2 related to degradation of heme; and the mRNAs that code for NR1I3 and NR1I2, which are transcription factors for some hepatic drug metabolizing enzyme.

Test No. 1:
In the experiment, MRA, or IL-6, or IL-6R were added to the each well of the 24-well plates containing hepatocytes in the combinations shown below; and the hepatocytes were exposed to the drugs for 72 hours.

Assay No.	1	2	3	4	5	6	7	8	9	10	11	12
MRA	×	L	M	H	×	×	×	H	L	×	×	×
IL-6	×	×	×	×	L	M	H	H	H	M	×	×
sIL-6R	×	×	×	×	×	×	×	×	×	○	○	×

H: The drug-supplemented solution containing the drug at the high concentration was added to the culture medium.

M: The drug-supplemented solution containing the drug at the medium concentration was added to the culture medium.

L: The drug-supplemented solution containing the drug at the low concentration was added to the culture medium.

○: The sIL-6R-supplemented solution was added to the culture medium.

×: No drug was added.

For the positive control, the phenobarbital-supplemented solution was added to the culture medium in Assay No. 12.

Test No. 2:
The drugs were added to the each well of the 24-well plates containing hepatocytes in the combinations shown below.

Assay No. 13: IL-6 at the medium concentration, 48 hours; then IL-6 at the medium concentration plus MRA at the high concentration, 72 hours
Assay No. 14: IL-6 at the medium concentration, 48 hours; then IL-6 at the medium concentration, 72 hours
Assay No. 15: IL-6 at the medium concentration, 48 hours; then no drug added, 72 hours
Assay No. 16: IL-6 at the medium concentration, 48 hours
Assay No. 17: No drug added, 48 hours
Assay No. 18: No drug added, 120 hours

At the end of incubation, hepatocytes were collected and total RNA was isolated and stored. mRNA expression levels for a particular P450 were quantified by a RT-PCR method.

Test Nos. 1 and 2 in human hepatocyte were performed 5 times each. The mean and standard deviation of the change ratio for expression level were calculated for each assay item.

In Test No. 1 in human hepatocyte, 3 wells of the 24-well plate were used for Assay No. 1, 2 wells were used for each of Assay Nos. 2 to 11, and 1 well was used for Assay No. 12. In Test No. 2 in human hepatocyte, 3 wells were used for each assay.

The mean of the normalized amounts was calculated for every assay in which several wells were used, and that mean value was used to calculate the change ratio for expression level.

Assay No. 1 was the control for Assay Nos. 2 to 12, Assay No. 18 was the control for Assay Nos. 13 to 15, and Assay No. 17 was the control for Assay No. 16.

Concentrations of IL-6 and MRA used in the experiment are listed below:

	Low	Medium	High
IL-6	0.02 ng/mL	0.5 ng/mL	12.5 ng/mL
MRA	1 ng/mL	0.5 µg/mL	250 µg/mL

Reviewer's Note: Monitoring IL-6 levels in clinical studies showed that IL-6 increased following MRA administration. IL-6 levels in RA patients are variable. For example, in Study LRO300 it was determined to be 3.2 to 923.6 ng/mL. High IL-6 concentration (12.5 ng/mL) used in this study could be seen in some RA patients. Cmax for MRA at 8 mg/mL was around 200 µg/mL at steady-state, corresponding to high MRA concentrations used in this study.

Results:

Test No. 1 (72 hour incubation):

Table 1 Expression level of cytochrome P450 and related mRNAs in human hepatocyte after treatment of MRA, IL-6 and sIL-6R.

	CYP2D6	CYP1A2	CYP2B6	CYP3A4
Assay No. 1	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Assay No. 2	0.96 ± 0.34	0.70 ± 0.13	0.76 ± 0.20	0.78 ± 0.16
Assay No. 3	0.83 ± 0.20	0.76 ± 0.14	0.84 ± 0.18	1.37 ± 0.54
Assay No. 4	1.27 ± 0.48	0.96 ± 0.38	1.27 ± 0.42	2.02 ± 1.66
Assay No. 5	1.18 ± 0.36	0.92 ± 0.36	1.34 ± 0.45	1.33 ± 0.48
Assay No. 6	1.69 ± 0.29	1.03 ± 0.31	1.08 ± 0.36	0.79 ± 0.14
Assay No. 7	0.67 ± 0.28	0.18 ± 0.13	0.28 ± 0.12	0.06 ± 0.07
Assay No. 8	0.68 ± 0.42	0.76 ± 0.23	0.92 ± 0.34	0.95 ± 0.82
Assay No. 9	0.76 ± 0.29	0.21 ± 0.19	0.28 ± 0.15	0.06 ± 0.08
Assay No. 10	1.33 ± 0.64	0.65 ± 0.21	0.72 ± 0.26	0.58 ± 0.11
Assay No. 11	1.59 ± 1.25	1.02 ± 0.62	1.04 ± 0.57	1.05 ± 0.51
Assay No. 12	0.84 ± 0.25	0.73 ± 0.32	195.30 ± 127.86	14.49 ± 8.99

	CYP2C19	CYP2C9	CYP2E1
Assay No. 1	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Assay No. 2	0.38 ± 0.13	1.49 ± 0.84	0.87 ± 0.29
Assay No. 3	0.27 ± 0.10	1.79 ± 0.82	0.98 ± 0.38
Assay No. 4	1.28 ± 0.77	1.89 ± 0.88	1.09 ± 0.41
Assay No. 5	2.86 ± 0.94	1.32 ± 0.43	1.12 ± 0.66
Assay No. 6	3.76 ± 2.02	1.15 ± 0.49	1.47 ± 0.45
Assay No. 7	0.43 ± 0.29	0.58 ± 0.25	1.28 ± 0.58
Assay No. 8	0.96 ± 0.87	1.44 ± 0.63	0.73 ± 0.34
Assay No. 9	0.29 ± 0.29	0.84 ± 0.65	1.57 ± 0.96
Assay No. 10	1.30 ± 1.07	2.16 ± 1.05	1.09 ± 0.36
Assay No. 11	4.66 ± 2.41	1.52 ± 0.86	0.93 ± 0.26
Assay No. 12	40.51 ± 39.51	1.94 ± 2.06	0.14 ± 0.16

	HMOX1	HMOX2	NR1I3	NR1I2
Assay No. 1	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Assay No. 2	0.93 ± 0.22	1.42 ± 0.66	0.83 ± 0.08	0.72 ± 0.17
Assay No. 3	0.90 ± 0.11	1.36 ± 0.58	0.98 ± 0.53	0.78 ± 0.20
Assay No. 4	0.92 ± 0.18	1.33 ± 0.29	1.23 ± 0.81	1.20 ± 0.68
Assay No. 5	0.99 ± 0.19	1.21 ± 0.45	1.30 ± 0.37	1.13 ± 0.29
Assay No. 6	1.15 ± 0.13	1.51 ± 0.62	1.27 ± 0.36	1.48 ± 0.69
Assay No. 7	2.06 ± 0.45	1.98 ± 0.78	0.61 ± 0.33	0.29 ± 0.07
Assay No. 8	0.82 ± 0.16	1.68 ± 0.81	0.81 ± 0.41	0.63 ± 0.27
Assay No. 9	2.02 ± 0.72	1.54 ± 0.75	0.90 ± 1.14	0.29 ± 0.09
Assay No. 10	0.87 ± 0.19	1.28 ± 0.66	1.14 ± 0.86	0.79 ± 0.39
Assay No. 11	0.86 ± 0.19	1.67 ± 1.15	0.97 ± 0.51	0.86 ± 0.28
Assay No. 12	1.85 ± 1.13	1.48 ± 1.21	1.02 ± 0.69	0.78 ± 0.09

Each value represents the mean ± SD
Assay No. 1: control
Assay No. 2, 3, 4: MRA 1 ng/mL, 0.5 or 250 µg/mL
Assay No. 5, 6, 7: IL-6 0.02, 0.5 or 12.5 ng/mL
Assay No. 8, 9: IL-6 12.5 ng/mL with MRA 250 µg/mL (No. 8) or 1 ng/mL (No. 9)
Assay No. 10, 11: 200 ng/mL sIL-6R with (No. 10) or without (No. 11) 0.5 ng/mL IL-6
Assay No. 12: Phenobarbital

After incubation with IL-6 for 72 hours at 0.5 ng/mL, no marked changes were observed in mRNA expression except that CYP3A4 mRNA levels decreased (Table 1, Assay No. 6). At a higher IL-6 concentration (12.5 ng/mL), the expression levels of the mRNAs for CYP1A2, CYP2B6, CYP3A4, CYP2C9, CYP2D6, and CYP2C19 decreased, and that decrease was particularly pronounced for CYP3A4 (Table 1, Assay No. 7). Co-incubation with tocilizumab at high concentrations (250 µg/mL) prevented the reduction of mRNA levels for all CYP isoenzymes (Table 1, Assay No. 8), while tocilizumab at a low concentration (1 ng/mL) showed no effect (Table 1, Assay No. 9).

Phenobarbital, which was used as the positive control in Test No. 1, was found to induce the expression of the mRNAs that code for CYP3A4, CYP2B6, and CYP2C19.

Test No. 2: (Incubate IL-6 first for 48 hours then add MRA incubate another 72 hours)

Table 2 Expression level of cytochrome P450 and related mRNA in human hepatocyte after treatment of MRA and IL-6.

	CYP2D6	CYP1A2	CYP2B6	CYP3A4
Assay No. 13	1.20 ± 0.68	2.22 ± 0.80	3.41 ± 1.39	1.80 ± 0.44
Assay No. 14	1.07 ± 0.55	0.58 ± 0.39	1.07 ± 0.59	0.66 ± 0.31
Assay No. 15	1.21 ± 0.66	0.75 ± 0.35	1.54 ± 0.70	0.88 ± 0.46
Assay No. 16	1.02 ± 0.45	0.54 ± 0.21	1.28 ± 0.66	0.81 ± 0.63
Assay No. 17	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Assay No. 18	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00

	CYP2C19	CYP2C9	CYP2E1
Assay No. 13	4.34 ± 1.74	1.01 ± 0.54	1.71 ± 0.82
Assay No. 14	0.69 ± 0.28	0.71 ± 0.20	1.78 ± 0.40
Assay No. 15	1.55 ± 1.03	1.03 ± 0.49	1.39 ± 0.53
Assay No. 16	1.13 ± 0.35	0.69 ± 0.31	0.96 ± 0.30
Assay No. 17	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Assay No. 18	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00

	HMOX1	HMOX2	NR1I3	NR1I2
Assay No. 13	1.03 ± 0.45	0.82 ± 0.60	1.03 ± 0.42	1.48 ± 0.62
Assay No. 14	1.59 ± 0.69	1.55 ± 1.06	0.89 ± 0.18	0.87 ± 0.41
Assay No. 15	1.37 ± 0.51	1.07 ± 0.77	1.03 ± 0.24	1.03 ± 0.33
Assay No. 16	1.47 ± 0.80	1.53 ± 0.94	0.98 ± 0.15	1.16 ± 0.53
Assay No. 17	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Assay No. 18	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00

Each value represents the mean ± SD
Assay No. 13: IL-6 48 hr, IL-6 + MRA 72 hr
Assay No. 14: IL-6 48 hr, IL-6 72 hr
Assay No. 15: IL-6 48 hr, no treatment 72 hr
Assay No. 16: IL-6 48 hr
Assay No. 17: Control for 48 hr culture
Assay No. 18: Control for 120 hr culture

The restorative effect of MRA on the expression levels of CYP mRNAs after those levels were changed by IL-6 was investigated. The expression levels of the mRNAs for CYP1A2, CYP3A4, CYP2C19, and CYP2C9 were decreased by exposure to IL-6 (0.5 ng/mL) for 120 hours (48 hours plus 72 hours) (Table 2, Assay No. 15). However, after exposure first to IL-6 at that concentration for 48 hours and then to IL-6 at that concentration plus MRA (250 μg/mL) for 72 hours, the IL-6-induced decrease in the expression level of the mRNA for CYP2C9 was prevented, and the expression levels of the mRNAs for CYP1A2, CYP3A4, and CYP2C19 increased (Table 2, Assay No. 13). The data may suggest that P450 mRNA levels in RA patients in the presence of MRA could be higher than those in healthy subjects.

Conclusions: In conclusion, IL-6 was found to affect the expression levels of several hepatic drug metabolizing enzymes in this *in vitro* study using human hepatocytes. It caused a pronounced reduction in the expression level of the mRNA that codes for CYP3A4 in particular. On the other hand, the results of this study show that the presence of MRA with IL-6 either prevented or moderated those effects of IL-6 on the hepatic drug metabolizing enzyme expression levels, and in some cases increased drug metabolizing enzyme expression levels compared to control.

4.2.5 Study MRA220JP: Drug Interaction Study of MRA in Patients with Rheumatoid Arthritis–Effects of Inhibition of IL-6 Signal Transduction on CYP3A4 and CYP2C19

Study Period: January 14, 2005 to August 16, 2005 b(4)
Investigators:
Study Site:

Objective: The effects of MRA-induced inhibition of IL-6 signal transduction on drug metabolizing enzymes were studied in rheumatoid arthritis (RA) patients. Using dextromethorphan hydrobromide and omeprazole as probe drugs for CYP3A4 and CYP2C19, respectively, the effects on these enzymes were studied by comparing the blood pharmacokinetics of dextromethorphan and its metabolites or omeprazole before and after infusion of MRA. For CYP2C19, the effects in extensive metabolizers (EM) and poor metabolizers (PM) were compared. Safety and efficacy were also assessed.

Study Rationale: IL-6 is reported to inhibit the expression of cytochrome P450 (CYP). The results of an *in vitro* study (Study ADM 03-0155) suggested that the levels of expression of CYP3A4, CYP2C19 and other enzymes are affected when IL-6 signal transduction is inhibited. Hence, it was decided to compare the pharmacokinetics of dextromethorphan, a substrate for CYP3A4, and omeprazole, a substrate for CYP2C19, before and after administration of MRA to assess the effect of MRA-induced inhibition of IL-6 signal transduction on metabolizing enzymes (CYPs).

Reviewer's Note: Dextromethorphan is not considered a good CYP3A4 probe substrate (it is mainly metabolized by CYP2D6 to form the major metabolite, dextrorphan. Dextrophan is further metabolized by CYP3A4). Although omeprazole is considered a probe substrate for CYP2C19, it is also metabolized by CYP3A4. Formation of the sulfone metabolite and 3-OH-OME is mediated by CYP3A4, whereas 5-OH-OME and 5'-O-desmethyl-OME are mainly formed by CYP2C19 with some contribution from CYP3A4. Because MRA may affect multiple P450s as indicated by in vitro study results,, other metabolism pathways for dextromethorphan or omeprazole need to be taken into considerations for data interpretation.

Methodology: Dextromethorphan hydrobromide 30 mg or omeprazole 10 mg was given orally on Day 0 and Day 14, and MRA 8 mg/kg was administered in a single intravenous infusion (duration of infusion: 1 hour) on Day 7.

Investigational product: MRA (Tocilizumab [recombinant]), Lot No.: MR4C05A

Dose and method of administration: 8 mg/kg MRA was intravenously drip infused over 1 hour. Dextromethorphan hydrobromide (Medicon® Tablets 15 mg × 2) was given orally. Omeprazole (Omepral® Tablets 10 × 1) was given orally.

Sample Collection:
a) Serum MRA concentration: On Day 7: Before and 1, 4 and 8 hours after administration of MRA. Day 8 (24 hours after completing infusion of MRA), Days 14, 21, 28, 25 and 42; and at withdrawal
b) Plasma dextromethorphan and metabolite concentration: On Days 0 and 14: Before and 1, 2, 3, 4, 6 and 8 hours after administration of dextromethorphan hydrobromide. On Days 1 and 15: 24 hours after administration of dextromethorphan hydrobromide.
c) Plasma omeprazole concentration: On Days 0 and 14: Before and 1, 2, 3, 4, 6 and 8 hours after administration of omeprazole. Days 1 and 15: 24 hours after administration of omeprazole.

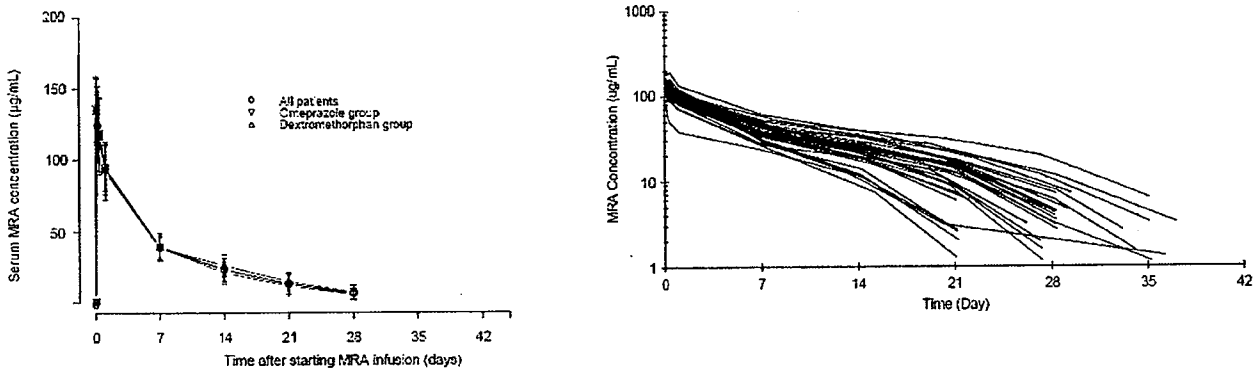
Subjects:
Dextromethorphan hydrobromide patients (CYP3A4 group): 13 patients
Omeprazole patients: CYP2C19-PM group: 5 patients, and CYP2C19-EM group: 13 patients.
Patients in the CYP2C19-EM group with heterozygous polymorphisms *2 (mutation at position 681) or *3 (mutation at position 636) were handled as the CYP2C19-IM group. In this study, the number of patients in each group was 5 in the CYP2C19-PM group, 5 in the IM group and 8 in the EM group.

There were no major biases in the characteristics among the groups (Table 1).

Table 1. Characteristics of Groups.

	Dextromethrophan N=13	**Omeprazole**	
		CYP2C19-PM N= 5	**CYP2C19-EM N=13**
Age (yr)	49.7 (25-69)	49.8 (23-65)	50.1 (26-65)
Disease Duration (yr)	6.41 (1.3-20.9)	6.76 (1.7-10.8)	6 (0.7-20.7)
DAS28	6.38 (4.8-8.4)	6.59 (5.2-8.6)	6.24 (5.1-8.2)
Baseline ESR (mm/hr)	70.4 (27-135)	76.6 (34-130)	64.3 (18-124)
CRP (mg/dL)	3.655 (1.56-8.8)	5.72 (1.74-10.61)	5.02 (1.79-10.63)
Male:Female	1:12	2:3	3:10

Results:
Pharmacokinetics:
-MRA concentrations:
There was no difference in the time courses of the serum MRA concentration for each probe drug group (Figure 1 and Table 2).



Linear Scale Log scale

Figure 1. Serum MRA concentration in each probe drug group.

Table 2. Pharmacokinetic Parameters of Serum MRA Concentration.

Parameter	Unit	No. of patients	Arithmetic mean	SD	CV (%)	SEM	Median	Min	Max	Geometric mean	90% confidence interval	
											Upper	Lower
C_{max}	µg/mL	31	136.8	22.7	16.59	4.1	141.0	88.3	191.0	134.9	143.7	129.9
AUC_{last}	hr*µg/mL	31	20640.5	5748.6	27.85	1032.5	20098.2	9335.3	33176.8	19851.5	22392.9	18888.1
AUC_{inf}	hr*µg/mL	31	21456.2	5958.4	27.77	1070.2	21177.4	9825.3	35041.1	20649.6	23272.6	19639.9
T_{max}	hr	31	2.7	1.6	59.57	0.3	2.0	2.0	9.0	2.4	3.2	2.2
$t_{1/2}$	hr	31	135.8	25.7	18.91	4.6	136.4	86.5	203.5	133.4	143.6	128.0
MRT	hr	31	206.7	41.4	20.04	7.4	205.2	132.3	315.6	202.6	219.3	194.1
k_{el}	1/hr	31	0.0053	0.0011	20.07	0.0002	0.0051	0.0034	0.0080	0.0052	0.0056	0.0050
CL	mL/hr/kg	31	0.404	0.125	30.92	0.022	0.378	0.228	0.814	0.387	0.442	0.366
V_d	mL/kg	31	76.04	17.06	22.44	3.06	72.45	56.83	147.78	74.58	81.24	70.84
V_{dss}	mL/kg	31	79.86	16.83	21.08	3.02	75.94	55.93	151.24	78.50	84.99	74.73

Seventeen of 31 patients received concomitant use of MTX. The presence or absence of concomitant use of MTX made no difference to the time course of serum MRA concentration (Figure 2).

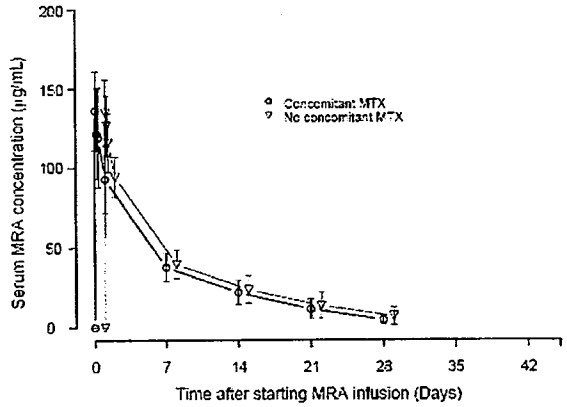


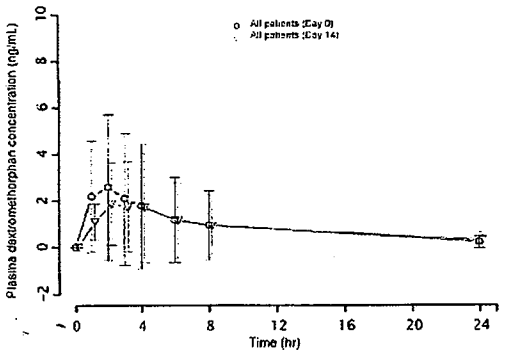
Figure 2. Serum MRA concentration in the presence or absence of concomitant use of MTX.

-Effect of MRA on Dextromethorphan and its Metabolites

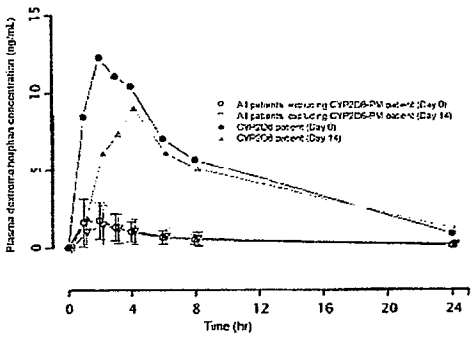
Note that in this study, the comparison was also displayed after excluding 1 patient (CYP2D6-PM; patient number 21008) in whom the measurement of SNPs for CYP2D6 showed a polymorphism of *10.

Both CYP2D6 and CYP3A4 are involved in the metabolism of dextromethorphan, the major metabolites of which are dextrorphan (mediated by CYP2D6) and 3-methoxymorphinan (mediated by CYP3A4), respectively. Furthermore, dextrorphan undergoes secondary metabolism by CYP3A4 and 3-methoxymorphinan by CYP2D6.

The time course of plasma dextromethorphan concentration before and after MRA infusion is shown in Figure 3 and summary pharmacokinetic parameters are presented in Table 3. The ratios of the geometric means of the pharmacokinetic parameters before and after MRA infusion and their 90% confidence intervals are presented in Table 4.



a. All patients



b. Separating one CYP2D6 PM from all other patients

Figure 3. Plasma dextromethorphan concentration (Mean ± SD).

Table 3. Pharmacokinetic Parameters of Plasma Dextromethorphan Concentration.

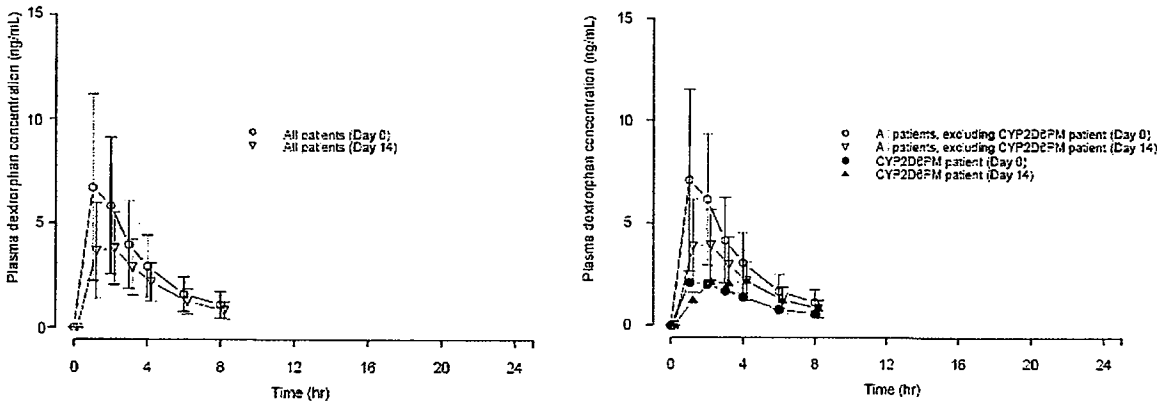
Timing	Parameter	Units	No. of patients	Arithmetic mean	SD	CV (%)	SEM	Median	Min	Max	Geometric mean	90% CI	
												Upper	Lower
Day 0	AUC_{inf}	hr*ng/mL	13	21.9	29.8	136.1	8.3	15.5	3.0	117.1	13.5	36.6	7.2
	AUC_{last}	hr*ng/mL	13	20.0	27.9	139.5	7.7	14.2	2.3	109.1	11.9	33.7	6.2
	CL/F	L/hr	13	2343	2017	86.1	559	1423	188	7305	1634	3340	1346
	C_{max}	ng/mL	13	2.76	3.19	115.3	0.88	1.75	0.50	12.28	1.81	4.34	1.19
	$t_{1/2}$	hr	13	6.66	2.07	31.1	0.57	6.78	3.10	9.50	6.31	7.69	5.64
	k_{el}	1/hr	13	0.118	0.050	42.2	0.014	0.102	0.073	0.224	0.110	0.142	0.093
	MRT	hr	13	9.36	2.68	28.6	0.74	10.04	5.26	13.30	8.97	10.68	8.04
	T_{max}	hr	13	1.85	0.55	29.8	0.15	2.00	1.00	3.00	1.76	2.12	1.58
	V_d/F	L	13	19558	12554	64.2	3482	13179	1646	40085	14865	25764	13352
Day 14	AUC_{inf}	hr*ng/mL	13	21.3	26.9	126.3	7.5	11.8	2.5	102.6	12.8	34.5	8.0
	AUC_{last}	hr*ng/mL	13	18.2	23.3	127.8	6.5	10.0	1.9	89.3	10.7	29.8	6.7
	CL/F	L/hr	13	2585	2347	90.8	651	1868	214	8633	1725	3745	1424
	C_{max}	ng/mL	13	2.17	2.36	109.2	0.66	1.38	0.39	9.00	1.44	3.34	1.00
	$t_{1/2}$	hr	13	7.63	2.10	27.5	0.58	7.98	3.51	10.03	7.30	8.67	6.60
	k_{el}	1/hr	13	0.101	0.040	39.7	0.011	0.087	0.069	0.198	0.095	0.120	0.081
	MRT	hr	13	11.08	2.63	23.7	0.73	11.89	6.41	14.27	10.76	12.38	9.79
	T_{max}	hr	13	2.23	0.93	41.5	0.26	2.00	1.00	4.00	2.06	2.69	1.77
	V_d/F	L	13	23585	14457	64.2	4010	25224	2369	46744	18161	30731	16439

Table 4. Changes in the Pharmacokinetic Parameters of Plasma Dextromethorphan Concentration Before and After MRA Infusion.

Parameter	Ratio*	Estimate	90% CI	
			Lower	Upper
AUC_{inf}	Day 14/Day 0	0.948	0.816	1.100
AUC_{last}	Day 14/Day 0	0.899	0.776	1.042
CL/F	Day 14/Day 0	1.055	0.909	1.226
C_{max}	Day 14/Day 0	0.794	0.658	0.959
MRT	Day 14/Day 0	1.199	1.140	1.261
V_d/F	Day 14/Day 0	1.222	1.041	1.434
k_{el}	Day 14/Day 0	0.864	0.829	0.900
Parameter	Difference†			
$t_{1/2}$	Day 14-Day 0	0.969	0.700	1.238
T_{max}	Day 14-Day 0	0.382	0.004	0.761

Dextromethrophan exposure was a little lower after MRA infusion (AUC was similar, Cmax was ~20% lower).

More effect from MRA infusion was seen for the metabolite, dextrophan (Figure 4 and Table 5).



a. All patients b. Separating one CYP2D6 PM from all other patients

Figure 4. Plasma dextrophan concentration (Mean ± SD).

The AUC_{inf} of the plasma dextrorphan concentration was 30.2 ± 16.5 hr•ng/mL (Mean ± SD) before MRA infusion and 20.4 ± 9.1 hr•ng/mL after MRA infusion, and the ratio of the geometric means (90% confidence interval) was 0.705 (0.592 to 0.838). AUC_{last} was 27.5 ± 16.6 hr•ng/mL before MRA infusion and 17.9 ± 9.0 hr•ng/mL after MRA infusion, and the ratio of the geometric means (90% confidence interval) was 0.689 (0.566 to 0.840). C_{max} was 7.45 ± 4.32 ng/mL before MRA infusion and 4.36 ± 2.04 ng/mL after MRA infusion, and the ratio of the geometric means (90% confidence interval) was 0.628 (0.527 to 0.748). These pharmacokinetic parameters decreased after MRA infusion.

Table 5. Changes in the Pharmacokinetic Parameters of Plasma Dextrorphan Before and After MRA Infusion.

Parameter	Ratio*	Estimate	90% CI	
			Lower	Upper
AUC_{inf}	Day 14/Day 0	0.705	0.592	0.838
AUC_{last}	Day 14/Day 0	0.689	0.566	0.840
CL/F	Day 14/Day 0	1.419	1.193	1.689
C_{max}	Day 14/Day 0	0.628	0.527	0.748
MRT	Day 14/Day 0	1.054	0.963	1.155
V_d/F	Day 14/Day 0	1.401	1.199	1.637
k_{el}	Day 14/Day 0	1.013	0.884	1.161
Parameter	Difference†			
$t_{1/2}$	Day 14-Day 0	−0.081	−0.510	0.348
T_{max}	Day 14-Day 0	0.460	−0.059	0.980

* Ratio of the geometric means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

† Difference of the arithmetic means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

The plasma 3-methoxymorphinan concentration was BLQ in more than half the patients at all measurement times, therefore summary statistics such as the mean values at each measurement time were not calculated.

-Effect of MRA on Omeprazole

PK profiles and parameters for omeprazole in CYP2C19 EM, IM and PM before and after MRA infusion are shown in Figure 5 and Table 6.

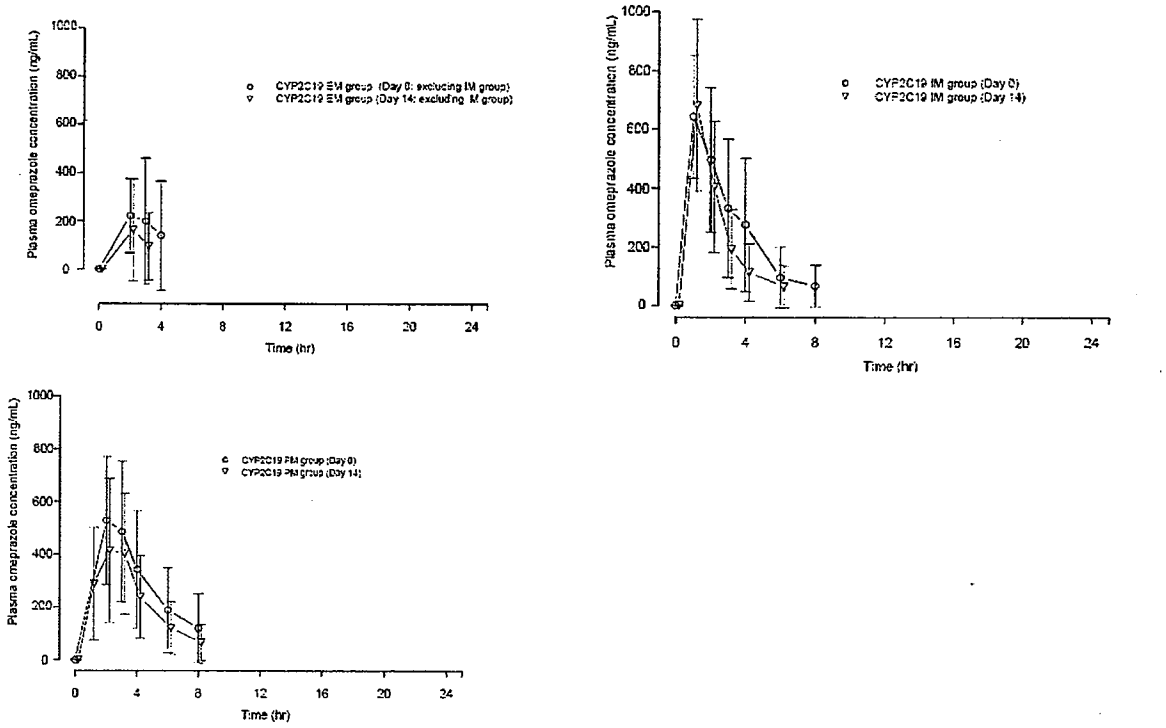


Figure 5. Time course of plasma omeprazole concentration before and after MRA infusion (CYP2C19-PM, IM and EM groups).

Table 6. Pharmacokinetic Parameters of Plasma Omeprazole Concentration before (Day 0) and after (Day 14, 7 days after) MRA Infusion.

CYP2C19-EM:

Target patients	Day	Parameter	Unit	No. of patients	Arithmetic mean	SD	CV (%)	SEM	Median	Min	Max	Geometric mean	90% CI	
													Upper	Lower
CYP2C19-EM group: 8 patients	Day 0	AUC_{inf}	hr*ng/mL	7	1099.1	1206.5	109.8	456.0	658.9	325.9	3783.3	789.9	1985.2	213.0
		AUC_{last}	hr*ng/mL	8	844.1	909.3	107.7	321.5	608.5	8.6	2966.0	423.3	1453.1	235.0
		CL/F	L/hr	7	15.53	8.97	0.06	3.39	15.18	2.64	30.69	12.66	22.12	8.94
		C_{max}	ng/mL	8	417.2	216.6	51.9	76.6	468.6	17.2	741.5	299.3	562.3	272.1
		$t_{1/2}$	hr	7	1.06	0.76	72.18	0.29	0.69	0.49	2.67	0.89	1.62	0.50
		k_{el}	1/hr	7	0.879	0.406	46.177	0.153	1.008	0.260	1.420	0.776	1.177	0.581
		MRT	hr	7	2.89	1.58	54.75	0.60	2.41	1.50	5.91	2.58	4.05	1.73
		T_{max}	hr	7	1.1	0.8	72.2	0.3	0.7	0.5	2.7	0.9	1.6	0.5
		V_d/F	L	7	17.09	5.96	0.0	2.25	17.03	10.18	28.95	16.30	21.47	12.71
	Day 14	AUC_{inf}	hr*ng/mL	4	789.3	974.9	123.5	487.4	314.3	277.8	2250.7	496.9	1936.4	-357.9
		AUC_{last}	hr*ng/mL	8	443.2	703.9	158.8	248.9	257.6	7.1	2159.6	157.4	914.7	-28.3
		CL/F	L/hr	4	26.23	14.94	0.06	7.47	32.24	4.44	36.00	20.13	43.80	8.65
		C_{max}	ng/mL	8	211.9	204.6	96.5	72.3	179.5	14.2	662.5	128.1	349.0	74.9
		$t_{1/2}$	hr	4	0.79	0.54	68.88	0.27	0.55	0.46	1.60	0.69	1.43	0.15
		k_{el}	1/hr	4	1.120	0.477	42.594	0.238	1.269	0.433	1.508	1.011	1.681	0.558
		MRT	hr	4	2.08	0.76	36.77	0.38	1.99	1.36	2.97	1.97	2.98	1.18
		T_{max}	hr	8	2.1	1.2	58.7	0.4	2.0	1.0	4.0	1.8	3.0	1.3
		V_d/F	L	4	21.20	7.39	0.0	3.69	23.98	10.27	26.56	19.90	29.89	12.51

CYP2C19-IM:

Target patients	Day	Parameter	Unit	No. of patients	Arithmetic mean	SD	CV (%)	SEM	Median	Min	Max	Geometric mean	90% CI	
													Upper	Lower
CYP2C19-IM group: 5 patients	Day 0	AUC_{inf}	hr*ng/mL	4	1923.2	1254.7	65.2	627.4	1497.8	982.3	3714.9	1665.9	3399.6	446.7
		AUC_{last}	hr*ng/mL	5	1461.6	1101.4	75.4	492.6	1076.4	266.1	3160.3	1099.6	2511.6	411.5
		CL/F	L/hr	4	6.77	3.39	0.05	1.69	7.10	2.69	10.18	6.00	10.75	2.78
		C_{max}	ng/mL	5	585.9	271.2	46.3	121.3	618.4	179.8	881.3	515.5	844.4	327.3
		$t_{1/2}$	hr	4	1.42	0.79	55.36	0.39	1.10	0.90	2.59	1.29	2.35	0.50
		k_{el}	1/hr	4	0.578	0.221	38.284	0.111	0.635	0.268	0.774	0.537	0.838	0.318
		MRT	hr	4	3.49	1.56	44.78	0.78	3.45	2.03	5.05	3.22	5.33	1.65
		T_{max}	hr	5	2.4	1.5	62.7	0.7	2.0	1.0	4.0	2.0	3.8	1.0
		V_d/F	L	4	11.31	1.95	0.0	0.98	11.42	9.26	13.16	11.19	13.61	9.02
	Day 14	AUC_{inf}	hr*ng/mL	5	1206.9	958.4	79.4	428.6	1084.7	295.7	2795.9	933.0	2120.6	293.2
		AUC_{last}	hr*ng/mL	5	1123.5	860.8	76.6	385.0	1046.5	272.9	2526.7	874.3	1944.2	302.8
		CL/F	L/hr	5	14.04	11.81	0.08	5.28	9.22	3.58	33.81	10.72	25.29	2.78
		C_{max}	ng/mL	5	556.7	321.4	57.7	143.7	615.2	120.5	894.3	450.7	863.1	250.3
		$t_{1/2}$	hr	5	1.16	0.62	53.69	0.28	0.90	0.75	2.26	1.06	1.75	0.56
		k_{el}	1/hr	5	0.696	0.231	33.210	0.103	0.767	0.307	0.922	0.654	0.917	0.476
		MRT	hr	5	2.85	1.07	37.64	0.48	2.92	1.61	4.09	2.68	3.87	1.83
		T_{max}	hr	5	1.2	0.6	53.7	0.3	0.9	0.8	2.3	1.1	1.7	0.6
		V_d/F	L	5	20.00	15.95	0.1	7.13	12.02	9.03	47.63	16.39	35.20	4.79

CYP2C19-PM:

Target patients	Day	Parameter	Unit	No. of patients	Arithmetic mean	SD	CV (%)	SEM	Median	Min	Max	Geometric mean	90% CI	
													Upper	Lower
CYP2C19-PM group: 5 patients	Day 0	AUC_{inf}	hr*ng/mL	5	2723.3	2014.4	74.0	900.9	2004.6	1372.0	6289.5	2318.9	4643.8	802.8
		AUC_{last}	hr*ng/mL	5	2545.8	2032.7	79.8	909.0	1814.6	1141.7	6143.4	2110.3	4483.7	607.9
		CL/F	L/hr	5	4.81	2.06	42.9	0.92	4.99	1.59	7.29	4.31	6.78	2.84
		C_{max}	ng/mL	5	612.1	221.1	36.1	98.9	580.9	322.1	928.8	578.4	823.0	401.3
		$t_{1/2}$	hr	5	2.43	1.05	43.23	0.47	2.19	1.53	4.19	2.27	3.43	1.43
		k_{el}	1/hr	5	0.322	0.110	34.147	0.049	0.316	0.166	0.452	0.305	0.427	0.217
		MRT	hr	5	4.88	1.69	34.61	0.75	4.49	2.79	7.46	4.65	6.49	3.27
		T_{max}	hr	5	2.0	0.7	35.4	0.3	2.0	1.0	3.0	1.9	2.7	1.3
		V_d/F	L	5	15.05	6.36	42.3	2.84	12.62	9.60	25.91	14.15	21.09	8.97
	Day 14	AUC_{inf}	hr*ng/mL	5	1903.5	1066.3	56.0	476.9	1437.6	1282.5	3789.7	1731.5	2920.2	886.9
		AUC_{last}	hr*ng/mL	5	1679.1	775.9	46.2	347.0	1353.1	1243.4	3056.6	1572.2	2418.9	939.4
		CL/F	L/hr	5	6.18	2.11	34.1	0.94	6.96	2.64	7.80	5.78	8.19	4.17
		C_{max}	ng/mL	5	563.5	171.5	30.4	76.7	509.6	419.6	853.2	545.6	727.0	400.1
		$t_{1/2}$	hr	5	1.94	0.52	26.54	0.23	1.74	1.52	2.82	1.89	2.43	1.45
		k_{el}	1/hr	5	0.374	0.080	21.410	0.036	0.399	0.246	0.457	0.366	0.450	0.297
		MRT	hr	5	3.92	1.22	30.99	0.54	3.57	2.68	5.45	3.78	5.08	2.76
		T_{max}	hr	5	1.8	0.8	46.5	0.4	2.0	1.0	3.0	1.6	2.6	1.0
		V_d/F	L	5	16.07	3.12	19.4	1.40	16.98	10.75	19.00	15.79	19.05	13.10

Table 7. Changes in the Pharmacokinetic Parameters of Plasma Omeprazole Concentration Before and After MRA Infusion.

CYP2C19-EM Group:

Parameter	Ratio*	Estimate	90% CI	
			Lower	Upper
AUC_{inf}	Day 14/Day 0	0.723	0.664	0.788
AUC_{last}	Day 14/Day 0	0.651	0.485	0.874
CL/F	Day 14/Day 0	1.383	1.270	1.506
C_{max}	Day 14/Day 0	0.692	0.550	0.870
MRT	Day 14/Day 0	0.885	0.712	1.100
V_d/F	Day 14/Day 0	1.136	0.987	1.309
k_{el}	Day 14/Day 0	1.190	1.072	1.319
Parameter	Difference†			
$t_{1/2}$	Day 14-Day 0	-0.421	-0.882	0.040
T_{max}	Day 14-Day 0	0.125	-0.842	1.092

* Ratio of the geometric means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

† Difference of the arithmetic means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

CYP2C19-IM Group:

Parameter	Ratio*	Estimate	90% CI	
			Lower	Upper
AUC_{inf}	Day 14/Day 0	0.875	0.767	0.999
AUC_{last}	Day 14/Day 0	0.905	0.805	1.018
CL/F	Day 14/Day 0	1.142	1.001	1.304
C_{max}	Day 14/Day 0	0.943	0.821	1.084
MRT	Day 14/Day 0	0.923	0.698	1.220
V_d/F	Day 14/Day 0	1.071	0.892	1.286
k_e	Day 14/Day 0	1.080	1.009	1.157
Parameter	Difference†			
$t_{1/2}$	Day 14-Day 0	-0.219	-0.391	-0.047
T_{max}	Day 14-Day 0	-0.807	-2.217	0.603

* Ratio of the geometric means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

† Difference of the arithmetic means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

CYP2C19-PM Group:

Parameter	Ratio*	Estimate	90% CI	
			Lower	Upper
AUC_{inf}	Day 14/Day 0	0.881	0.780	0.995
AUC_{last}	Day 14/Day 0	0.880	0.762	1.017
CL/F	Day 14/Day 0	1.135	1.005	1.282
C_{max}	Day 14/Day 0	0.975	0.830	1.145
MRT	Day 14/Day 0	0.914	0.832	1.004
V_d/F	Day 14/Day 0	1.049	0.912	1.206
k_e	Day 14/Day 0	1.083	0.987	1.187
Parameter	Difference†			
$t_{1/2}$	Day 14-Day 0	-0.484	-1.060	0.092
T_{max}	Day 14-Day 0	-0.200	-0.998	0.598

* Ratio of the geometric means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

† Difference of the arithmetic means for patients in whom the pharmacokinetic parameters both before and after MRA infusion were calculated

-mRNA levels:

Changes in the level of expression of CYP3A4, CYP2C19, CYP2D6, IL-6 and IL-6 receptor mRNA were measured on Days 0, 7, 21 and 42 in the 18 patients receiving omeprazole. The expression of mRNA was calculated as a ratio relative to the selected universal control, the total mRNA in human peripheral leucocytes. The mean value (n=3) of the ratio of the signal intensity of mRNA (Cy5/Cy3) at each measurement time for each patient was standardized by dividing by the mean value (n=3) for Day 0, using base 2 log-transformed values. The change in the level of

expression of mRNA of the CYPs (CYP2C19, CYP3A4 and CYP2D6) did not exceed 2-fold in any patients.

The change in the level of expression of mRNA of IL-6 exceeded 2-fold in 2 patients (patient numbers 11001 and 11013) and decreased to less than 1 of 2 in 1 patient (patient number 11017).

For the mRNA of IL-6 receptor, the changes in exon 7-8, exon 9 and exon 10 were similar in all patients. There were no patients for whom the change exceeded 2-fold for both probes. The IL-6 receptor is composed of 10 different exons, and researchers have reported that it is expressed as soluble IL-6 receptor when exon 9 is defective, and as membrane-bound IL-6 receptor when non-defective.

Discussion and Conclusion:
-Dextromethorphan and metabolites
For dextromethorphan, it has been reported that the AUCinf of dextromethorphan in healthy subjects after administration of dextromethorphan hydrobromide 60 mg ranged from 35.1 ± 13.9 to 42.0 ± 13.2 hr•ng/mL (Mean ± SE), Cmax 5.2 ± 1.8 to 5.8 ± 1.7 ng/mL (Medicon® 15 mg Tablets [package insert]) (at the dose of 30 mg administered in the present study, AUCinf was projected to be 17.55 to 21 hr•ng/mL and Cmax was 2.6 to 2.9 ng/mL).

As the plasma dextrorphan concentration ascertained in the present study was similar to the reported values in healthy adults (Table 8), it would appear that the total clearances of dextromethorpha by CYP2D6 and CYP3A4 in healthy adults are not different from those in RA patients. Furthermore, since the plasma dextromethorphan concentrations before and after MRA infusion were not substantially different, it would appear that MRA infusion has little effect on the total clearances of dextromethorpha by CYP2D6 and CYP3A4.

Table 8. Comparison of exposure of dextromethorphan obtained from this study vs. historical data in healthy subjects (30 mg dextromethorphan).

	Exposure in Healthy Subject (estimated from Medicon® 15 mg Tablets [package insert])	Exposure in RA patients (this Study) before MRA infusion
Mean AUCinf (hr•ng/mL)	17.55 to 21	21.9
Mean Cmax (ng/mL)	2.6 to 2.9	2.76

For dextrorphan, AUCinf has been reported to range from 3590.2 ± 209.9 to 3984.8 ± 200.8 hr•ng/mL (Mean ± SE) and Cmax 774.2 ± 54.3 to 879.1 ± 59.7 ng/mL (at the dose of 30 mg administered in the present study, AUCinf was 1795.1 to 1992.4 hr•ng/mL and Cmax was 387.1 to 439.55 ng/mL) in healthy subjects.

In contrast to the parent, the plasma dextrorphan concentration measured in this study was only a few percent of the reported value in healthy adults (Table 9).

Table 9. Comparison of exposure of dextrorphan obtained from this study vs. historical data in healthy subjects (30 mg dextromethorphan).

	Exposure in Healthy Subject (estimated from Medicon® 15 mg Tablets [package insert])	Exposure in RA patients (this Study) before MRA infusion
Mean AUCinf (hr•ng/mL)	1795 to 1992	30.2
Mean Cmax (ng/mL)	387 to 440	7.45

The fact that metabolite levels are low may be explained by downregulation of CYP enzymes in RA patients with increased IL-6 levels. The fact that parent levels are similar between healthy subjects and RA patients may indicate a compensatory pathway other than metabolism to eliminate dextrometrophan.

It is difficult to discretion effect of MRA on either CYP3A4 or CYP2D6 individually from this study. The Sponsor conducted another interaction study with simvastatin to determine effect of MRA on CYP3A4 (results pending).

-Omeprazole

After administration of omeprazole 10 mg to healthy adults, the AUC0-10hr was reported to be 480.7 ± 160.2 hr•ng/mL (Mean ± SE) and Cmax was 184.1 ± 31.5 ng/mL (Omeprazon® Tablets 10 mg/20 mg [package insert]). The AUC and Cmax values obtained before MRA infusion in each of the groups in this study were higher than those reported for healthy adults (Table 10). The data may be explained by downregulation of CYP enzymes in RA patients with increased IL-6 levels. The AUC and Cmax values obtained after MRA infusion were close to the reported values, the data may suggest that the expression of CYP2C19 was normalized by treatment with MRA. The effect of MRA seen in CYP2C19 IM and CYP2C19 EM may be attributed to the CYP3A4 pathways in these patients.

Table 10. Comparison of exposure of omeprazole obtained from this study vs. historical data in healthy subjects (10 mg omeprazole).

	Exposure in Healthy Subject (from Omeprazon® Tablets 10 mg/20 mg [package insert])	Exposure in RA patients (this Study) before MRA infusion CYP2C19 EM group	Exposure in RA patients (this Study) 7-days after single dose MRA infusion CYP2C19 EM group
Mean AUCinf (hr•ng/mL)	481 *	1099	783
Mean Cmax (ng/mL)	184	417.2	212

*AUC(0-10 hour). Omeprazole has short half-life there fore AUC(0-10h)≈AUCinf.

In conclusion, the study provided *in vivo* evidence that MRA could modulate P450 enzyme levels by binding to IL-6 receptor. The exposure levels of P450 substrates can be altered following MRA administration (similar to induction effect). The P450 expression levels would determine the *in vivo* exposure for a drug that is a P450 substrate. It is not clear about the P450 enzyme expression levels in RA patients (who have elevated IL-6) with TCZ compared to those

in healthy subjects who have normal IL-6 levels. The effect may be CYP enzyme-dependent. And results from an *in vitro* study (Section 4.2.4) suggested that CYP3A4 may be the most affected.

Drug interactions mediated by MRA would have clinical implication for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted based on response measurements (e.g., warfarin) or drug monitoring (e.g., cyclosporine or theophylline) where a decrease of up to 50% could become clinically relevant. In addition, depending on the P4503A4 level change, decrease in oral contraceptive (CYP3A4) exposure is expected and may lead to decrease in efficacy.

4.3 Pharmacometrics Review

Office of Clinical Pharmacology

BLA	125276
Drug	Tocilizumab
Indication	*Rheumatoid Arthritis* Reducing signs and symptoms in adult patients with moderately to severely active disease
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram, Ph.D.
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Introduction

Tocilizumab (RO4877533, TCZ), also referred to as myeloma receptor antibody (MRA), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against the interleukin-6 (IL-6) receptor to inhibit the activity of IL-6.

Interleukin-6 is a pleiotropic pro-inflammatory multi-functional cytokine produced by a variety of cell types including lymphocytes, monocytes and fibroblasts. It binds to its soluble and membrane-bound receptors, and its interaction with glycoprotein 130 transduces intracellular signals that mediate gene activation and a wide range of biological activities. Interleukin-6 has been shown to be involved in such diverse physiological processes as stimulation of hemopoietic precursor cell growth and differentiation, proliferation of hepatic, dermal and neural cells, bone metabolism and lipid metabolism.

This application seeks approval for TCZ alone or in combination with methotrexate (MTX) or other disease modifying anti-rheumatic drugs (DMARDs) in the treatment of adult patients with moderate to severe active rheumatoid arthritis (RA).

Recommendations

The labeling statements derived from population pharmacokinetic analyses are acceptable.

Regulatory Issues

In the current submission, the sponsor conducted population PK, exposure-response (Efficacy, Safety) analysis.

The aim of this review is to verify the labeling statements derived based on these analyses.

Sponsor's Analysis

Population Pharmacokinetic Analysis

Data

The data included in the population pharmacokinetic analysis is shown in Table 1 below.

Table 1. Number of serum concentrations per study and per patient

Phase – Study Number – Study Title (shortened)	IV Dose Regimen (Starting Dose and Dosing Interval)	No. serum concentrations / No. Patients treated with TCZ
Phase III – WA17822 – Safety and efficacy of tocilizumab in combination with MTX therapy	4 or 8 mg/kg 1x/4 weeks	2342 / 396
Phase III – WA17824 – Safety and efficacy of tocilizumab monotherapy	8 mg/kg 1x/4 weeks	1154 / 338
Phase III – WA18062 – Safety and efficacy of tocilizumab in combination with MTX therapy	4 or 8 mg/kg 1x/4 weeks	1388 / 341
Phase III – WA18063 – Safety and efficacy of tocilizumab in combination with DMARD therapy	8 mg/kg 1x/4 weeks	2531 / 718

Model

A 2 compartment PK model with linear and nonlinear components for clearance provided good description of the data. The nonlinear elimination pathway of tocilizumab is believed to represent a target mediated clearance process due to the binding to IL-6R.

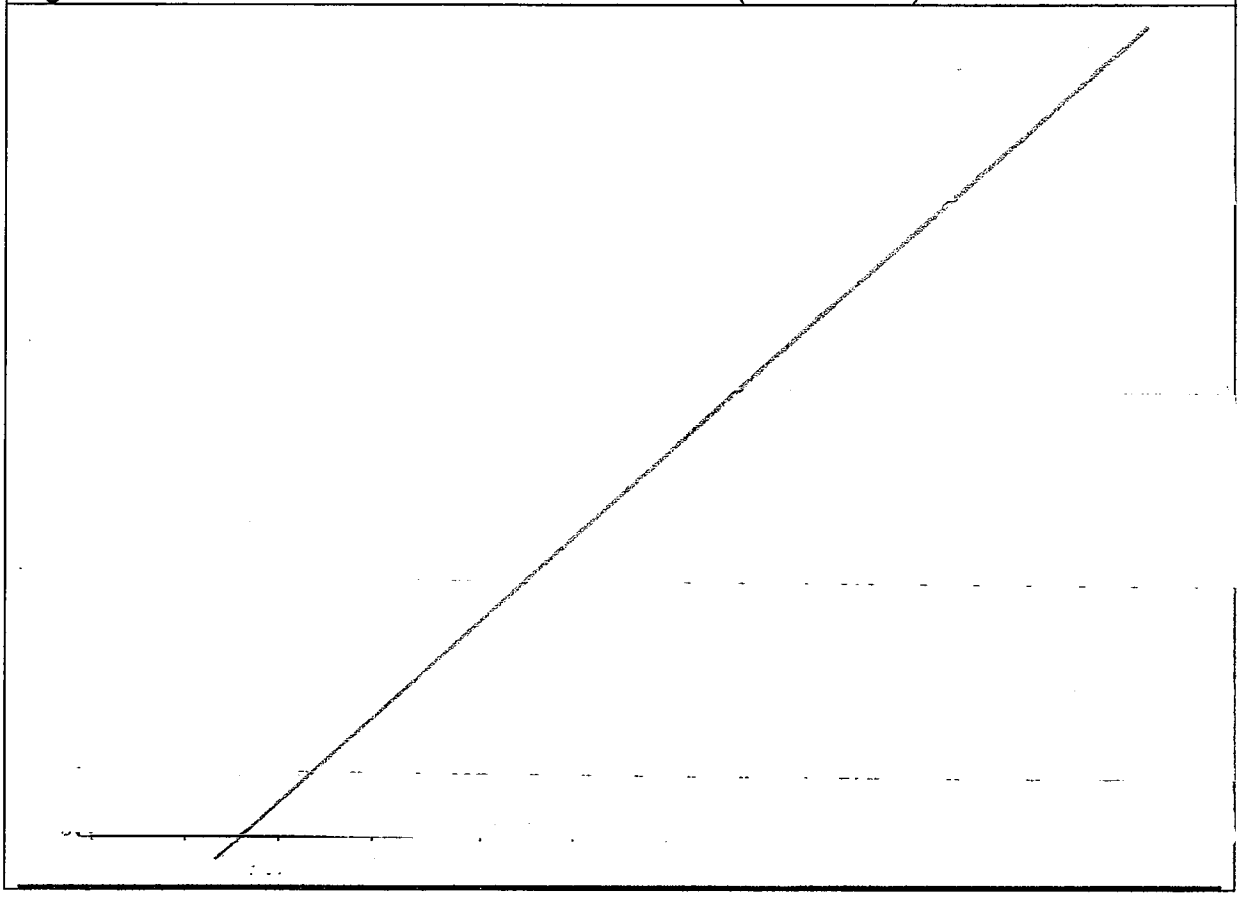
Covariates

The influence of covariates on the PK of tocilizumab was initially identified using GAM (Generalized Additive Modeling). These covariates were further evaluated using step-wise forward and backward selection method using NONMEM.

Results

Figure 1 shows the observed (symbols), individual predicted (solid line) and population predicted serum concentration (dotted lines) time course in few individual patients. A two compartment model including both a non-saturable (linear) and saturable (non-linear) elimination pathway described the pharmacokinetics of tocilizumab.

Figure 1. Individual serum concentration time course (linear Y-axis)



b(4)

Based on generalized additive modeling (GAM), there was no significant effect of concomitant medications such as celecoxib, chloroquine and derivatives, codeine and derivatives, diclofenac, ibuprofen and derivatives, meloxicam, methotrexate, naproxen and derivatives, paracetamol, prednisone and derivatives and tramadol on the pharmacokinetics of tocilizumab. The inclusion of rheumatoid factors (RF) as a covariate, which are usually low affinity IgM anti-IgG Fc auto-antibodies, was based on binding to the Fc region which could potentially impact antibody clearance.

Table 2. Covariates identified by GAM analysis	
Clearance (CL)	BSA (Body Surface Area), SEX, TOBA (Smoking), CRCL (Creatinine Clearance), PROT (Protein), BUN (Blood Urea Nitrogen), ALBU (Albumin), ESR (Erthrocyte Sedimentation Rate), HDL (High Density Lipoprotein), CMET (Concomitant Methotrexate) and the log- transformed RF (Rheumatoid Factor).
Volume of distribution of the central compartment (V1)	TOBA, RACE, PROT, AGE and ALBU.
Volume of distribution of the peripheral compartment (V2)	SEX, ALBU, CRCL and BUN.
Maximum elimination rate (VM)	SEX, TOBA, RACE, PROT, HDL, ALBU, BUN, CRCL, CFAC (Concomitant Folic Acid and Dervatives) and the log-transformed RF.

The estimates of the PK parameters based on the population pharmacokinetic analysis are shown in Table 3.

Table 3. NONMEM parameter values for final PK model (Source: Table 14, Page 32 from 1027775.pdf)

Parameter	Unit	Estimate	RSE (%) (*)
Fixed Effects			
CL	L/d (mL/h)	0.3 (12.5)	4.1
V1	L	3.5	1.8
Q	L/d (mL/h)	0.21 (8.75)	8.1
V2	L	2.9	5.0
VM	mg/d (mg/h)	7.5 (0.31)	5.8
KM	µg/mL	2.7	9.6
Between-patients variability			
CL	CV%	39	15 (**)
V1	CV%	37	14 (**)
V2	CV%	66	21 (**)
VM	CV%	54	20 (**)
Correlation CL-V1	-	0.55	18 (**)
Correlation CL-V2	-	-0.062	155 (**)
Correlation CL-VM	-	-0.47	28 (**)
Correlation V1-V2	-	0.52	32 (**)
Correlation V1-VM	-	0.22	36 (**)
Correlation V2-VM	-	0.21	53 (**)
Covariate Effects			
Effect of BSA on CL	-	0.67	14
Effect of SEX on CL	-	-0.16	15
Effect of HDL on CL	-	-0.17	30
Effect of LRF on CL	-	0.091	39
Effect of PROT on V1	-	-1.1	18
Effect of ALBU on V1	-	0.68	21
Effect of ALBU on VM	-	-0.43	31
Effect of CRCL on VM	-	0.23	14
Effect of TOBA on VM	-	0.11	26
Error Model			
σ1 (additive)	µg/mL	2.4	12
σ2 (proportional)	%	22	6.0

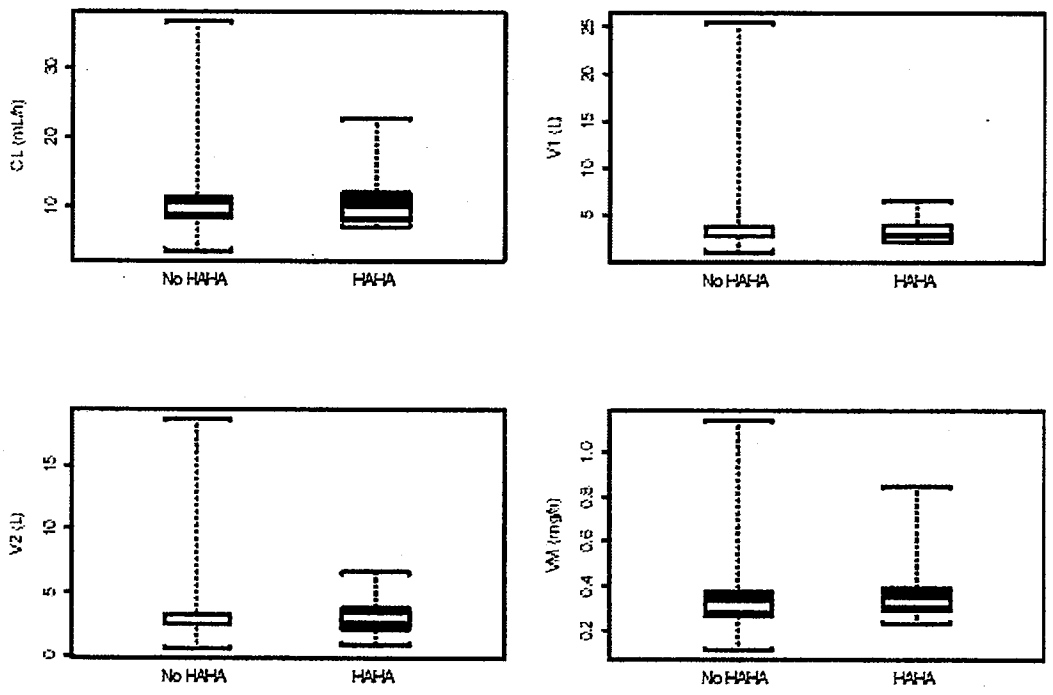
CL – drug clearance, V1 – central volume of distribution, Q – inter-compartmental clearance, V2 – peripheral volume of distribution, VM – maximum elimination rate, KM – Michaelis-Menten constant, BSA – body surface area, SEX – gender, HDL – HDL cholesterol, LRF – logarithm of rheumatoid factor, PROT – total protein, ALBU – albumin, CRCL – creatinine clearance, TOBA – smoking, CV -coefficient of variation, σ – standard error, RSE: Relative standard error of estimate, OFV: NONMEM Objective Function Value, *: obtained with a nonparametric bootstrap, **: RSE of the variance or covariance

Based on the data available as shown in Table 4, there was no effect of anti-tocilizumab HAHAs (Human Anti-Human Antibodies) on the PK of tocilizumab. Figure 2 shows the comparison of PK parameters in patients with HAHAs and without HAHAs.

Table 4. Summary of patients in the PK dataset tested positive for anti-tocilizumab (TCZ) human anti-human antibodies (HAHAs) in the confirmation assay by study, by dose and by visit

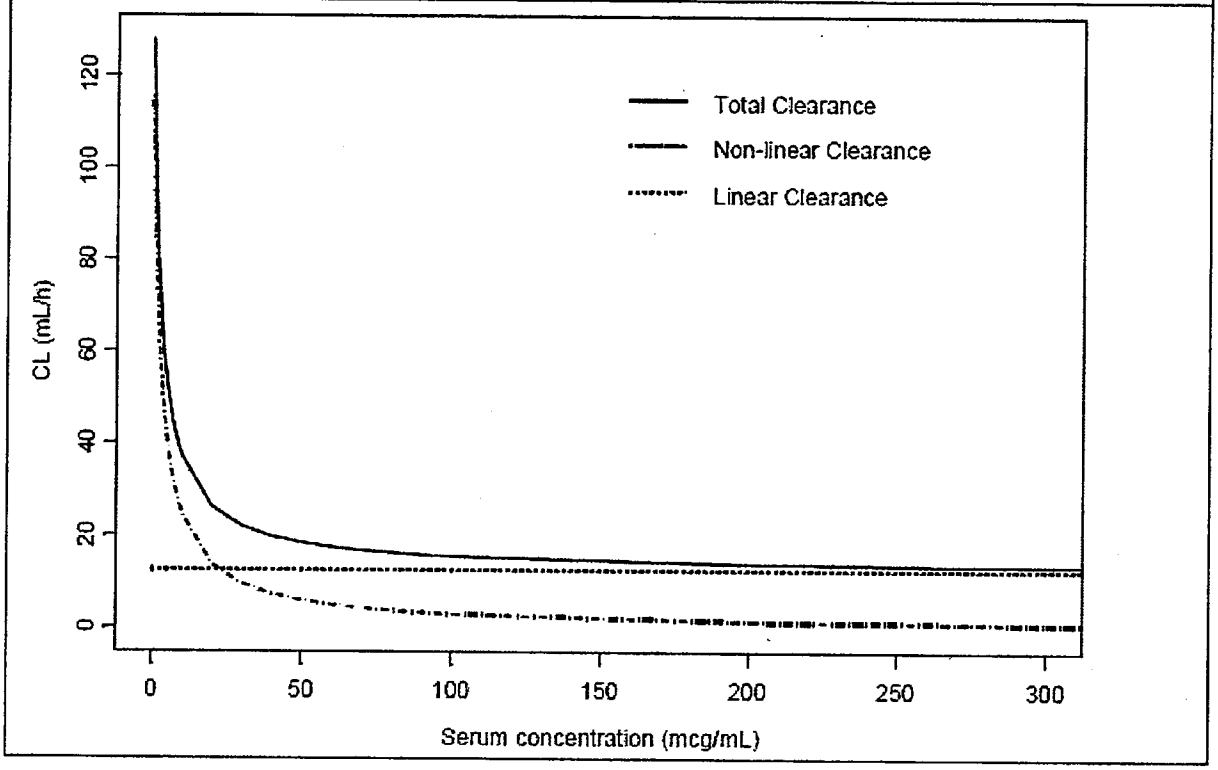
Presence of anti-TCZ HAHAs	WA17822		WA17824	WA18062		WA18063
	4 mg/kg	8 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg	8 mg/kg
Total number of Patients	2	3	1	0	5	7
Number of patients per visit						
Week 4		2	1		4	3
Week 8	2	2			1	3
Week 12	1				1	3
Week 20	1					
Week 24		1			3	5

Figure 2. Comparison of the individual PK parameters (posthocs) between patients where no HAHAs were detected and for patients where HAHAs were detected



The dependence of total clearance on tocilizumab serum concentrations, using population estimates of the linear (CL) and the nonlinear clearance (serum tocilizumab concentration ×VM/KM) components, is shown in Figure 3. The two components of the total clearance contribute equally to the elimination of tocilizumab for concentrations around 25 µg/mL. At very low concentrations, the nonlinear clearance represents almost the entire total clearance and is approximately 10-fold higher than the linear clearance. For concentrations above 50 µg/mL, the influence of the nonlinear clearance became negligible and the total clearance is dominated by the linear clearance.

Figure 3. Dependence of total, linear and nonlinear Clearance (CL) on tocilizumab serum concentrations



The time to steady state, accumulation ratio for Cmax, Cmin and AUC were determined using simulations due to nonlinear PK as shown in Figure 4, Table 5 and

Table 6. Accumulation ratios for AUC, Cmax and Cmin after 48 weeks of treatment with 4 and 8 mg/kg every 4 weeks

For Cmax, 90% of the steady-state was reached after the first infusion. For AUC, 90% of the steady-state was also reached after the first infusion for the 4 mg/kg dose, and after the second infusion for the 8 mg/kg dose. Due to the nonlinear part of CL of tocilizumab, it took longer to reach 90% of the steady-state for Cmin, with 4 and 5 months for the 4 and 8 mg/kg doses, respectively.

The accumulation ratios for AUC were relatively small: 1.11 and 1.22 for 4 and 8 mg/kg doses, respectively. The accumulation ratios were larger for the Cmin due to nonlinear CL: 1.96 and 2.35 for the 4 and 8 mg/kg doses, respectively. The smallest accumulation ratios were obtained for the Cmax: 1.02 to 1.06 for 4 and 8 mg/kg doses, respectively.

Figure 4. Simulated time-course of tocilizumab serum concentrations over 6 months of treatment at 4 and 8 mg/kg

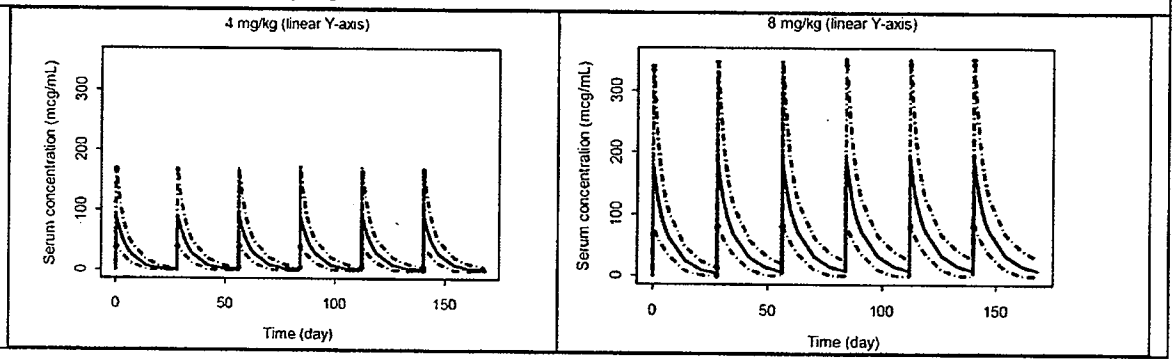


Table 5. Simulated mean (SD) AUC, Cmax and Cmin after 48 weeks of treatment with 4 and 8 mg/kg every 4 weeks

Week	AUC (103×µg/mL×h)		Cmax (µg/mL)		Cmin (µg/mL)	
	4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg
0	11.8 (5.0)	28.8 (11.6)	86.8 (40.9)	173.6 (81.9)	0.76 (0.91)	4.14 (4.29)
4	12.5 (5.4)	31.8 (13.3)	87.5 (41.2)	177.8 (83.8)	1.12 (1.43)	6.65 (6.75)
8	12.8 (5.6)	33.3 (14.2)	87.9 (41.3)	180.3 (84.7)	1.29 (1.71)	7.94 (8.11)
12	12.9 (5.7)	34.0 (14.7)	88.1 (41.4)	181.6 (85.2)	1.38 (1.87)	8.64 (8.92)
16	13.0 (5.8)	34.4 (15.0)	88.2 (41.4)	182.3 (85.4)	1.42 (1.96)	9.05 (9.43)
20	13.0 (5.8)	34.6 (15.1)	88.2 (41.4)	182.7 (85.5)	1.45 (2.02)	9.30 (9.77)
24	13.0 (5.8)	34.7 (15.3)	88.2 (41.4)	182.9 (85.5)	1.47 (2.06)	9.46 (10.00)
28	13.0	34.8 (15.3)	88.2 (41.4)	183.1	1.48 (2.08)	9.56 (10.15)

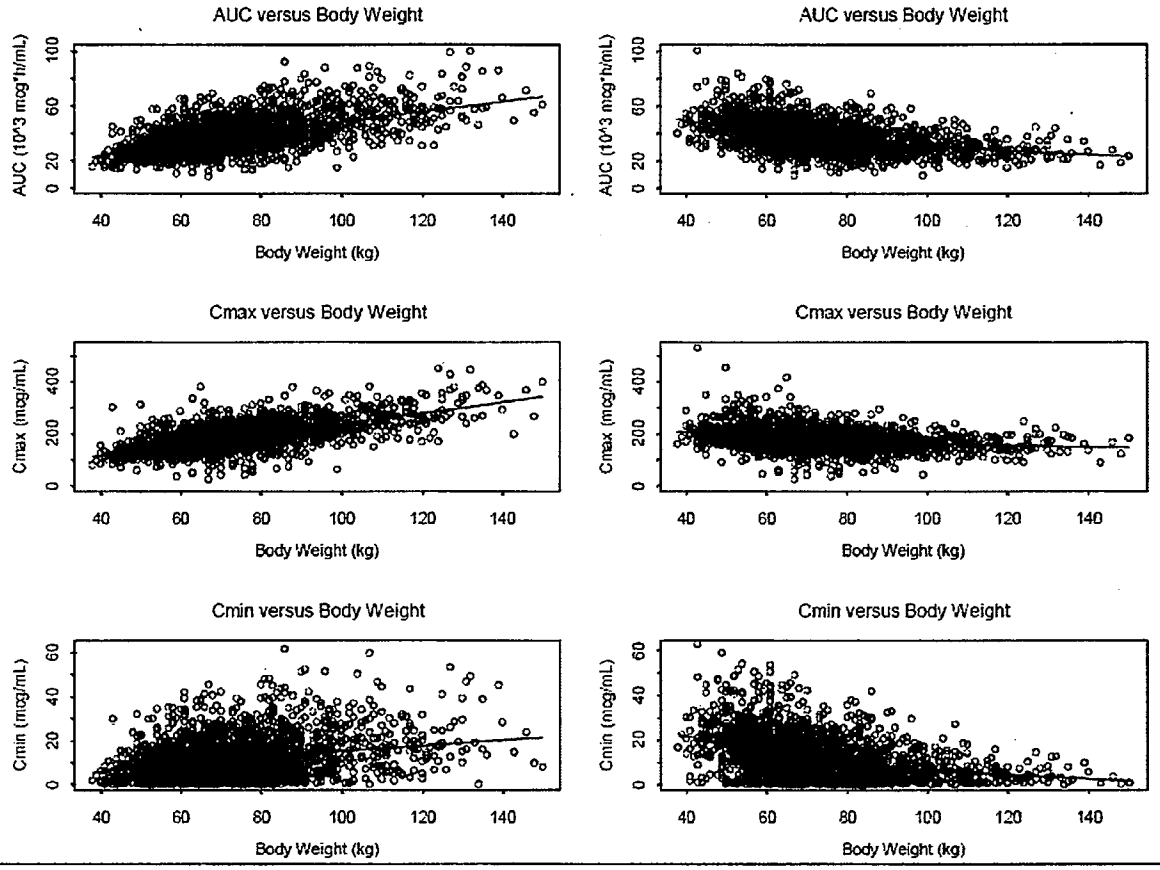
		(5.8)			(85.6)			
	32	13.0 (5.8)	34.9 (15.4)	88.2 (41.4)	183.2 (85.6)	1.48 (2.10)	9.63 (10.26)	
	36	13.0 (5.8)	34.9 (15.4)	88.2 (41.4)	183.2 (85.6)	1.49 (2.11)	9.68 (10.35)	
	40	13.0 (5.8)	35.0 (15.5)	88.3 (41.4)	183.4 (85.6)	1.49 (2,12)	9.71 (10.41)	
	44	13.0 (5.8)	35.0 (15.5)	88.3 (41.4)	183.4 (85.6)	1.49 (2.13)	9.74 (10.45)	

Table 6. Accumulation ratios for AUC, Cmax and Cmin after 48 weeks of treatment with 4 and 8 mg/kg every 4 weeks

AUC (µg/mL×h)		Cmax (µg/mL)		Cmin (µg/mL)	
4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg
1.11	1.22	1.02	1.06	1.96	2.35

The impact of body weight based dosing vs body weight independent dosing (one flat dose for all weight groups) on AUC, Cmax and Cmin of Tocilizumab was evaluated using simulations. Figure 5 shows that the body weight based dosing does not ensure similar AUC in all body weight groups.

Figure 5. Comparison of the relationship between body weight and the steady-state tocilizumab secondary PK parameters (AUC, Cmax and Cmin) with a body weight dosing regimen (8 mg/kg - left panels) and with a flat dose (560 mg - right panels)



In terms of effectiveness (ACR20) response, the percentage of responders was lower in group of patients who weigh more than 100 kg compared to <60 kg and 60-100 kg (Source: Dr Joan Buenconsejo, Office of Biostatistics Review)

Table 7. Proportion of ACR20 responders at Week 24 by Treatment Group and Weight Category – Study WA18063

	ACR20		Placebo + DMARD	TCZ 8 mg/kg+DMARD	
	Weight	Overall % responder	N=413 101 (24%)	N=803 488 (61%)	
		< 60 kg % responder	n=98 17 (17%)	n=179 123 (69%)	
		60 – 100 kg % responder	n=281 76 (27%)	n=555 327 (59%)	
		> 100 kg % responder	n=34 8 (24%)	n=69 38 (55%)	

The sponsor conducted additional analysis to evaluate if the higher AUC, Cmax, Cmin resulted in higher safety related events. Figure 6 shows the plot of serious adverse events (SAEs) super classes versus the AUC of tocilizumab cumulated up to the time of occurrence of SAEs in patients treated with tocilizumab. The plots of all SAEs and of SAEs probably, possibly or remotely related to tocilizumab intake versus the Cmax of tocilizumab before the occurrence of SAEs in Figure 7. Based on visual examination of these figures it appears that there is no clear link between higher exposures and the safety events.

Figure 6. Occurrence of Serious Adverse Events versus cumulative AUC of tocilizumab

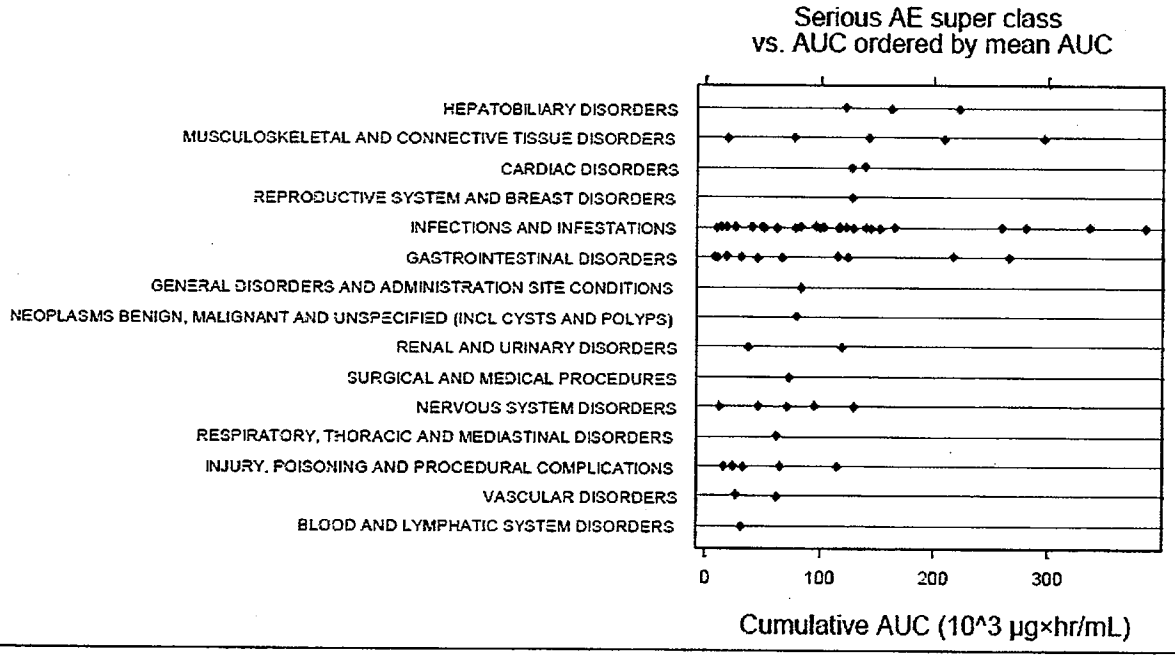


Figure 7. Plots of adverse events by nature versus the AUC(top), Cmax(bottom) of tocilizumab cumulated up to the time of occurrence of adverse events in patients treated with tocilizumab

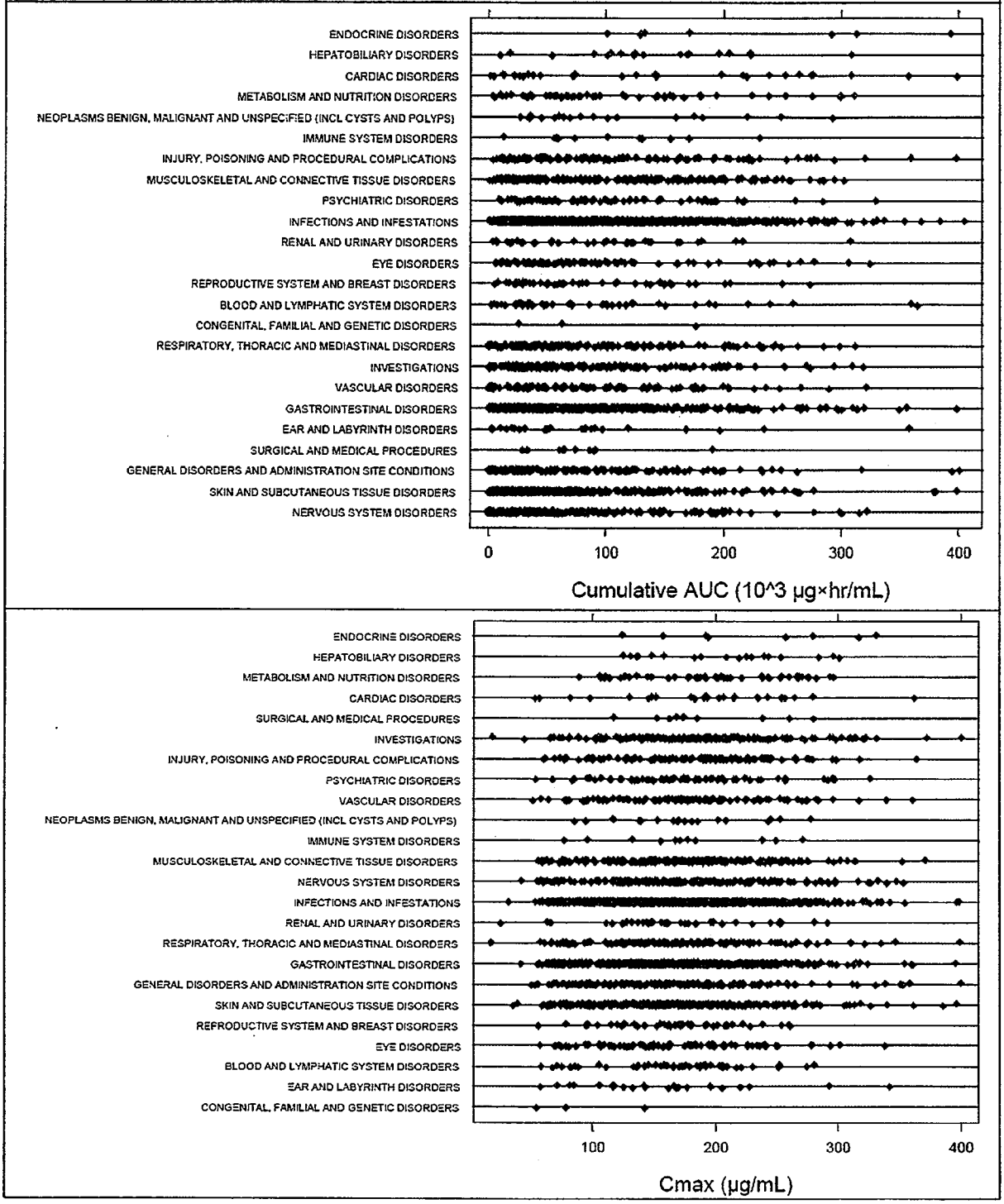


Table 8 shows the percentage of patients with adverse events in three weight groups (>100 kg, ≥ 60 to ≤100 kg, < 60kg). A trend towards higher occurrence of any adverse event in patients who weigh more than 100 kg is seen in 8 mg/kg+DMARD group. However, similar trend is also seen in Placebo+DMARD group.

Table 8. Overview of Adverse Events by Weight (6 Months Pooled Safety Population) (Source: Table 56, Page 220 in css.pdf)

AE	Placebo +DMARD N=1170	MTX N=284	MRA 4 mg/kg + MTX N=774	MRA 8 mg/kg + DMARD N=1582	MRA 8 mg/kg N=288
N					
> 100 kg	105	28	60	122	22
≥ 60 to ≤ 100 kg	776	181	525	1076	200
< 60 kg	285	74	185	378	63
Missing	4	1	4	6	3
Pts with any AE – n (%)					
> 100 kg	76 (72.4)	19 (67.9)	51 (85.0)	96 (78.7)	19 (86.4)
≥ 60 to ≤ 100 kg	482 (62.1)	136 (75.1)	370 (70.5)	780 (72.5)	153 (76.5)
< 60 kg	173 (60.7)	64 (86.5)	123 (66.5)	254 (67.2)	55 (87.3)
Pts with serious AE – n (%)					
> 100 kg	4 (3.8)	1 (3.6)	2 (3.3)	8 (6.6)	1 (4.5)
≥ 60 to ≤ 100 kg	46 (5.9)	6 (3.3)	30 (5.7)	70 (6.5)	9 (4.5)
< 60 kg	12 (4.2)	1 (1.4)	14 (7.6)	16 (4.2)	1 (1.6)
Pts with AEs leading to WD – n (%)					
> 100 kg	1	2 (7.1)	2 (3.3)	6 (4.9)	-
≥ 60 to ≤ 100 kg	17 (2.2)	10 (5.5)	23 (4.4)	52 (4.8)	8 (4.0)
< 60 kg	10 (3.5)	3 (4.1)	12 (6.5)	15 (4.0)	3 (4.8)
Pts with Infection – n (%)					
> 100 kg	43 (41.0)	10 (35.7)	30 (50.0)	57 (46.7)	9 (40.9)
≥ 60 to ≤ 100 kg	241 (31.1)	62 (34.3)	179 (34.1)	390 (36.2)	65 (32.5)
< 60 kg	90 (31.6)	34 (45.9)	60 (32.4)	143 (37.8)	24 (38.1)
Pts with serious infection – n (%)					
> 100 kg	-	1 (3.6)	1 (1.7)	5 (4.1)	1 (4.5)
≥ 60 to ≤ 100 kg	13 (1.7)	1 (0.6)	7 (1.3)	28 (2.6)	2 (1.0)
< 60 kg	4 (1.4)	-	5 (2.7)	5 (1.3)	1 (1.6)

Overall, the proposed dosing regimen based on body weight is reasonable inspite of higher exposures in higher body weight. Any dose adjustment algorithm that would ensure similar exposure in all weight groups might result in a lower ACR20 response that currently observed.

Reviewer's Analysis/Comments

The reviewer finds the population pharmacokinetic analysis conducted by the sponsor acceptable. The estimates of the base model for population PK were reproducible. However, the final model as developed by the sponsor resulted in ROUNDING ERRORS. The PK parameter estimates were similar to those reported by the sponsor with a different error message based on sponsor's output file. Since the labeling statements were derived based on the estimates from the base model, the reviewer created graphs to confirm the labeling statements. The reviewer did not further explore the reasons for the differences in NONMEM analysis error messages.

Labeling Statements

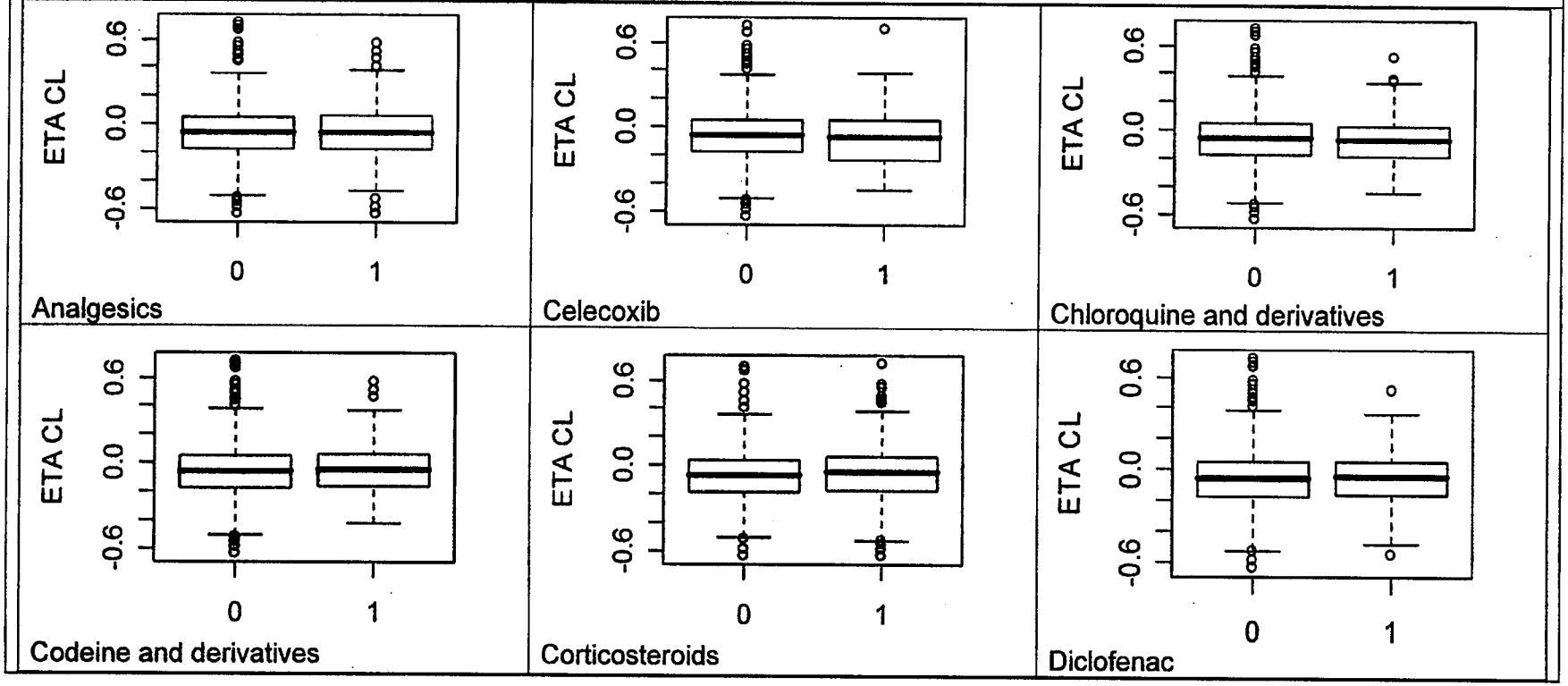
The following labeling statements are derived based on population pharmacokinetic analysis.

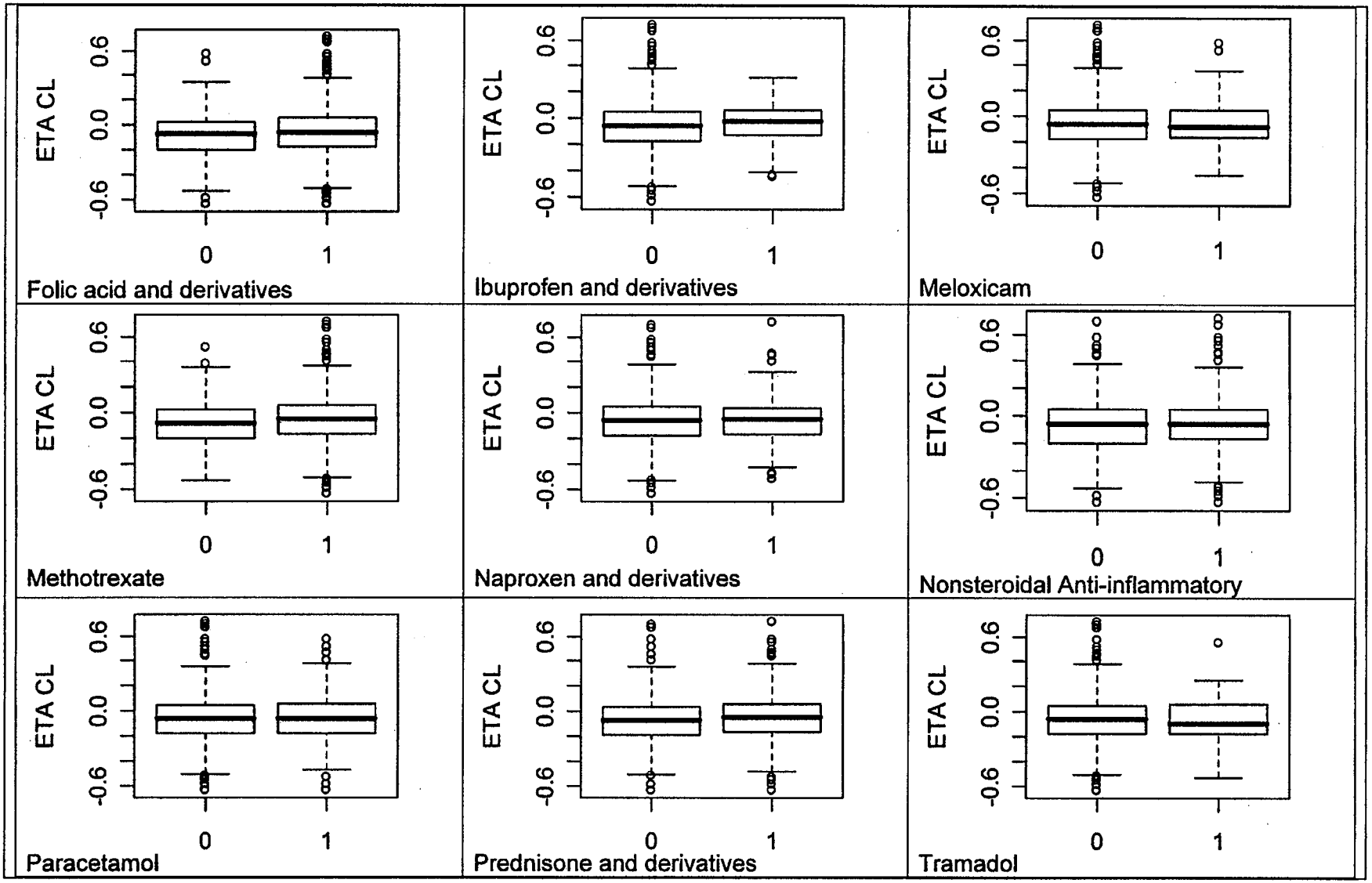
7 DRUG INTERACTIONS

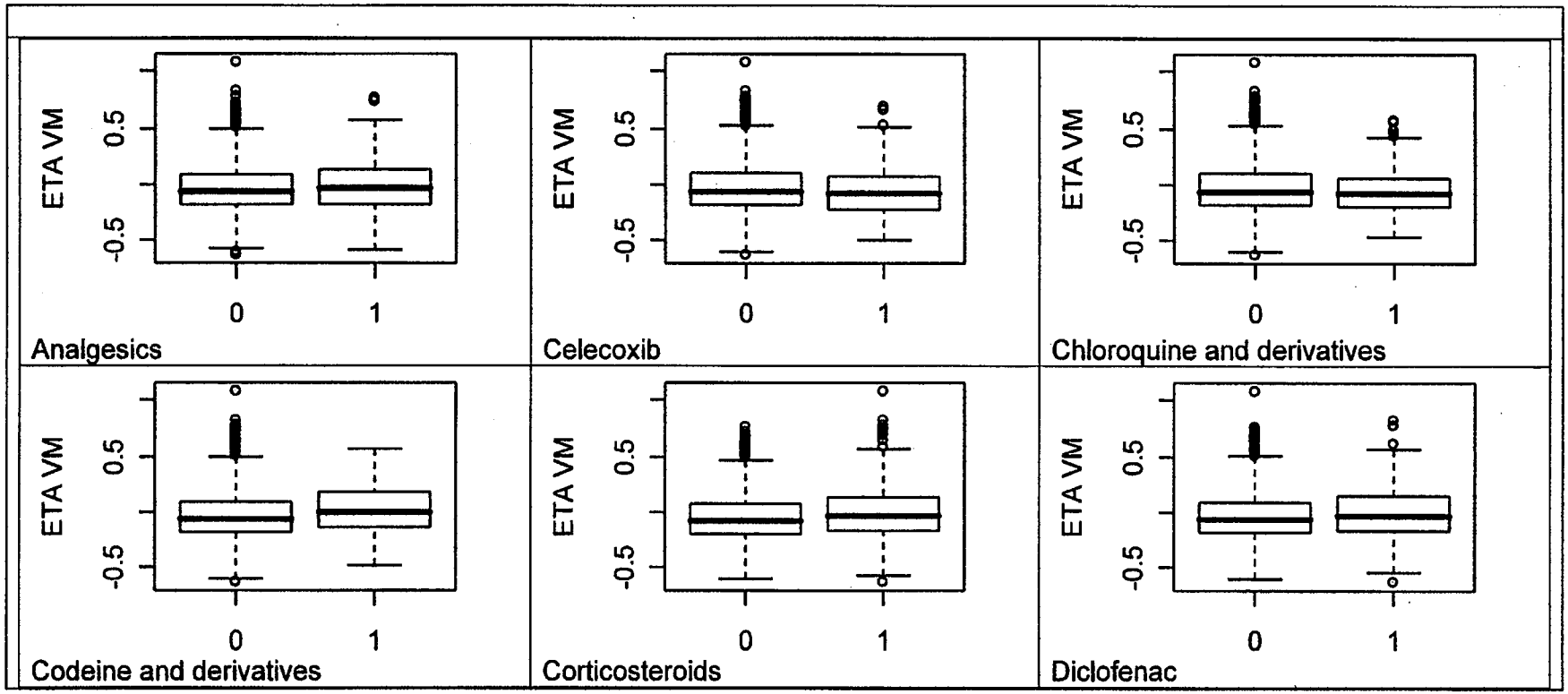
7.1 Other Drugs for Treatment of RA

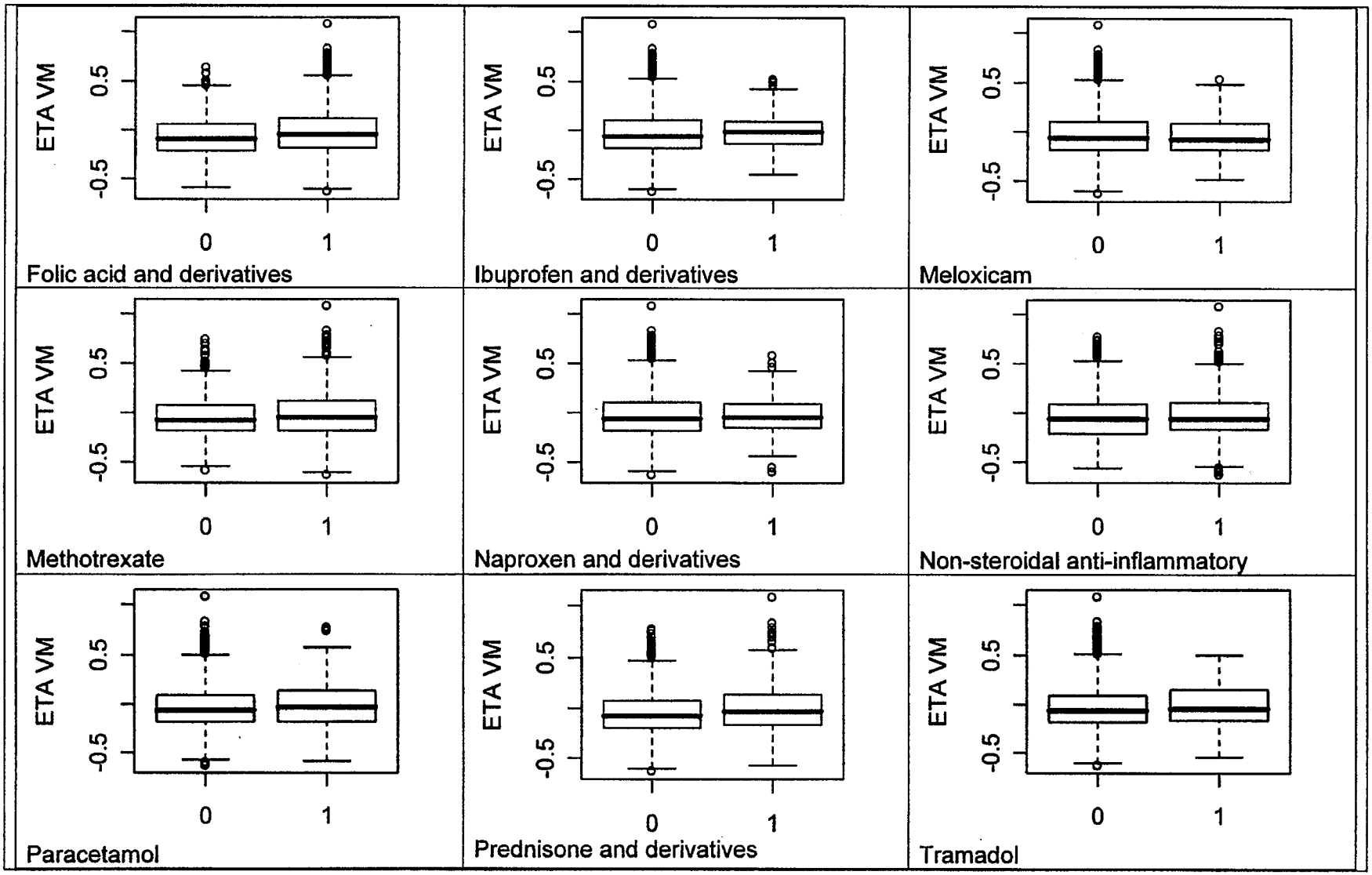
Population pharmacokinetic analyses revealed that concomitant use of medicinal products for rheumatoid arthritis such as methotrexate, cholorquine and derivatives, immunosuppressants (leflunomide, azathioprine), corticosteroids (prednisone and derivatives), folic acid and derivatives, non-steroidal anti-inflammatory drugs(naproxen, ibuprofen, cox-2 inhibitors (celecoxib), meloxicam, diclofenac), and analgesics (acetaminophen, codeine and derivatives, tramadol) did not influence the pharmacokinetics of tocilizumab.

Figure 8. Box plots showing comparison of ETACL in patients taking concomitant medications (1 on box plot X-axis) and not taking concomitant medications (0 on box plot X-axis)




ETA CL
0.6
0.0
-0.6
0
1
Folic acid and derivatives
Ibuprofen and derivatives
Meloxicam
Methotrexate
Naproxen and derivatives
Nonsteroidal Anti-inflammatory
Paracetamol
Prednisone and derivatives
Tramadol


ETA VM
0.5
-0.5
0
1
Analgesics
Celecoxib
Chloroquine and derivatives
Codeine and derivatives
Corticosteroids
Diclofenac


ETA VM
0.5
-0.5
0
1
Folic acid and derivatives
Ibuprofen and derivatives
Meloxicam
Methotrexate
Naproxen and derivatives
Non-steroidal anti-inflammatory
Paracetamol
Prednisone and derivatives
Tramadol

12.3 Pharmacokinetics

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis of 1793 rheumatoid arthritis patients treated with tocilizumab 4 and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (Cmin) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration (Cmax) increased dose-proportionally.

At steady-state, predicted AUC and Cmin were 2.7 and 6.5-fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

For doses of tocilizumab 8 mg/kg given every 4 weeks, the predicted mean (± SD) steady-state AUC, Cmin and Cmax of tocilizumab were 35000 ± 15500 h•mcg/mL, 9.74 ± 10.5 mcg/mL, and 183 ± 85.6 mcg/mL, respectively. The accumulation ratios for AUC and Cmax were 1.22 and 1.06, respectively. The accumulation ratio was higher for Cmin (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for Cmax, AUC, and Cmin, respectively.

Reviewer's Comments: The labeling statements are acceptable. They are based on simulation of 48 weeks of treatment with the two doses tested in Phase 3 (4 and 8 mg/kg) was performed with 10 replicates of the original NONMEM dataset (N=1793 per replicate) as shown in Figure 9.

Figure 9. Simulated mean (SD) AUC, Cmax and Cmin after 48 weeks of treatment with 4 and 8 mg/kg every 4 weeks. (Source: Table 21, Page 45 in 102775.pdf)

Week	AUC (10^3×µg/mL×h)		C_{max} (µg/mL)		C_{min} (µg/mL)	
	4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg
0	11.8 (5.0)	28.8 (11.6)	86.8 (40.9)	173.6 (81.9)	0.76 (0.91)	4.14 (4.29)
4	12.5 (5.4)	31.8 (13.3)	87.5 (41.2)	177.8 (83.8)	1.12 (1.43)	6.65 (6.75)
8	12.8 (5.6)	33.3 (14.2)	87.9 (41.3)	180.3 (84.7)	1.29 (1.71)	7.94 (8.11)
12	12.9 (5.7)	34.0 (14.7)	88.1 (41.4)	181.6 (85.2)	1.38 (1.87)	8.64 (8.92)
16	13.0 (5.8)	34.4 (15.0)	88.2 (41.4)	182.3 (85.4)	1.42 (1.96)	9.05 (9.43)
20	13.0 (5.8)	34.6 (15.1)	88.2 (41.4)	182.7 (85.5)	1.45 (2.02)	9.30 (9.77)
24	13.0 (5.8)	34.7 (15.3)	88.2 (41.4)	182.9 (85.5)	1.47 (2.06)	9.46 (10.00)
28	13.0 (5.8)	34.8 (15.3)	88.2 (41.4)	183.1 (85.6)	1.48 (2.08)	9.56 (10.15)
32	13.0 (5.8)	34.9 (15.4)	88.2 (41.4)	183.2 (85.6)	1.48 (2.10)	9.63 (10.26)
36	13.0 (5.8)	34.9 (15.4)	88.2 (41.4)	183.2 (85.6)	1.49 (2.11)	9.68 (10.35)
40	13.0 (5.8)	35.0 (15.5)	88.3 (41.4)	183.4 (85.6)	1.49 (2.12)	9.71 (10.41)
44	13.0 (5.8)	35.0 (15.5)	88.3 (41.4)	183.4 (85.6)	1.49 (2.13)	9.74 (10.45)

Elimination

The total clearance of tocilizumab is concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated to be

12.5 mL/h in the population pharmacokinetic analysis. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

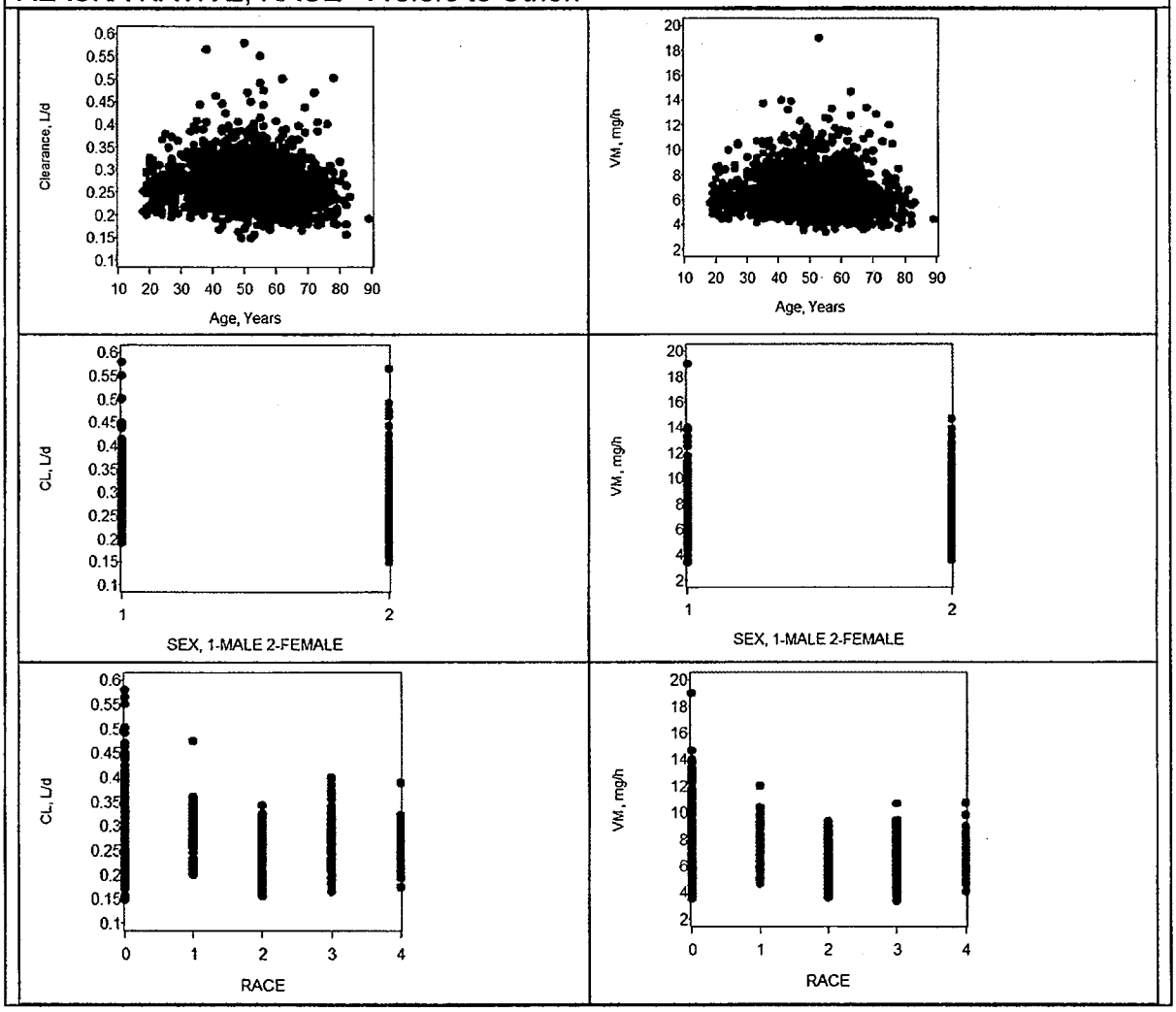
The t1/2 of tocilizumab is concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective t1/2 decreased with decreasing concentrations within a dosing interval from 13 days to 4 days.

Reviewer's Comments: The labeling statements are acceptable.

Pharmacokinetics in Special Populations
Population pharmacokinetic analyses in adult rheumatoid arthritis patients showed that age, gender and race did not affect the pharmacokinetics of tocilizumab.

Reviewer's Comments:
The labeling statements are acceptable. Figure 10 shows the relationship between PK parameters (CL and VM) and covariates (RACE, SEX and AGE). There is no need for dose adjustment based on these covariates.

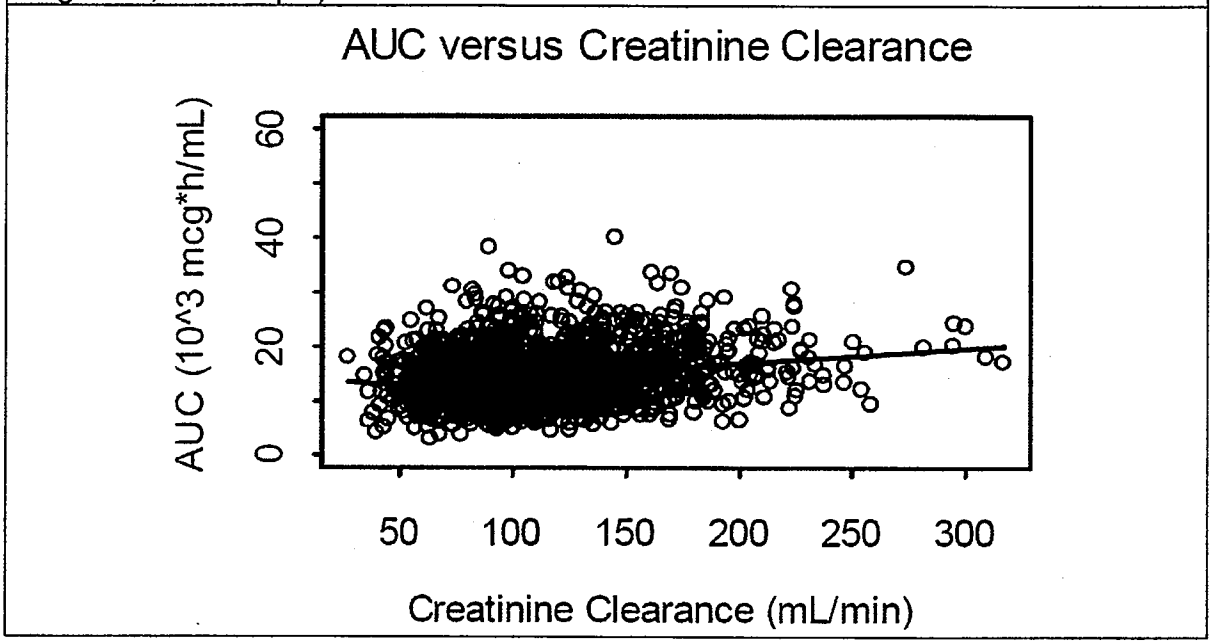
Figure 10. Relationship between clearance (linear) and VM (Maximum elimination rate, nonlinear) and covariates (Age, SEX, RACE). RACE=0 refers to White; RACE=1 refers to BLACK, RACE=2 refers to ASIAN, RACE=3 refers to AMERICAN INDIAN or ALASKA NATIVE, RACE=4 refers to Other.



Renal Impairment
No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.
Most patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ≥ 50 mL/min) did not impact the pharmacokinetics of tocilizumab.

Reviewer's Comments: This statement is based on the relationship shown in Figure 11. Although the X-axis shows creatinine clearance greater than 130 mL/min, values greater than 130 mL/min should be rounded to 130 mL/min. Although, the effect of renal function was a significant covariate on maximum elimination rate (VM) in population pharmacokinetic analysis, the AUC is not influenced significantly with changes with renal function.

Figure 11. Relationship between AUC and creatinine clearance (Source: Appendix 18, Page 416, 102775.pdf)



Sponsor conducted an exploratory study (MRA 221JP), to evaluate the impact of renal function on the pharmacokinetics of tocilizumab. Since tocilizumab is humanised IgG (Immunoglobulin G), its elimination from the body is presumably due in large part to metabolism in the reticuloendothelial systems of the liver, kidneys and spleen. In study MRA 221JP, RA (rheumatoid arthritis) patients with various degrees of renal function (10-80 mL/min; 4-Mild, 5-Moderate, 3-Severe, 2-Normal) were administered single dose of 8 mg/kg as a 1 hour infusion. Patients with severe renal impairment have 22% higher

AUC when compared to normal as shown in Figure 12 and Figure 13. A similar trend is also observed based on predicted AUC from population pharmacokinetic analysis as shown in Figure 11. Based on relationship between AUC and safety events as shown in Figure 6 and Figure 7, the observed increase in AUC in patients with severe renal function would not necessitate dose adjustment based on renal function.

Figure 12. Mean time course of Tocilizumab (MRA) concentrations in patients with mild, moderate and severe renal impairment.

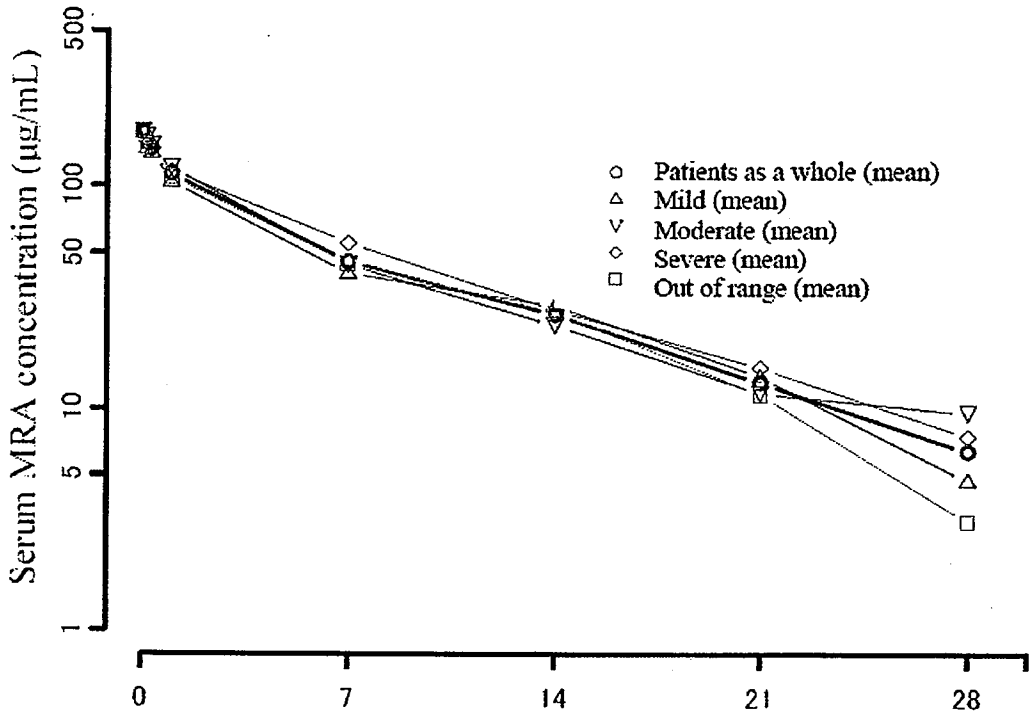
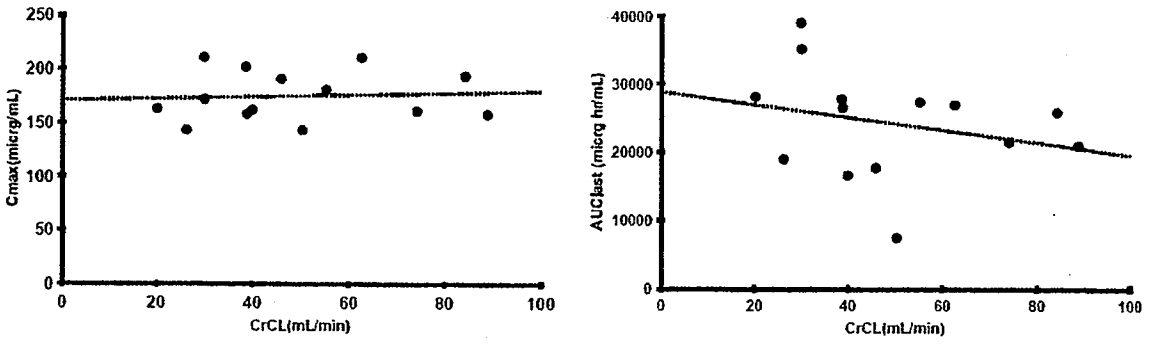


Figure 13. Relationship between Cmax, AUC of tocilizumab and renal function.



4.4 OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application/Biologics License Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125276	Brand Name	ACTEMRA®
OCP Division	DCP2	Generic Name	Tocilizumab
Medical Division	DAARP	Drug Class	Interleukin-6 (IL-6) receptor inhibitor
OCP Reviewers	Lei Zhang, Ph.D. Atul Bhattaram, Ph.D. (PM)	Indication(s)	For the treatment of: • Rheumatoid Arthritis (RA) - Reducing signs and symptoms in adult patients with moderately to severely active disease
OCP Team Leaders	Suresh Doddapaneni, Ph.D Jogarao Gobburu, Ph.D. (PM)	Dosage Form	Concentrate solution for intravenous infusion
		Dosing Regimen	8 mg/kg once every 4 weeks, alone or in combination with methotrexate or other DMARDs Dilute the dose to 100 mL and infusion over 1 hour (do not bolus or push)
Date of Submission	11/19/2007	Route of Administration	Intravenous infusion
Estimated Due Date of OCP Review	7/21/2008	Sponsor	Roche
PDUFA Due Date	9/18/2008	Priority Classification	1S
Division Due Date	8/19/2008		BB-IND 11,972

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	6 (26)	6	Including assays for antibodies and biomarkers
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
1) Healthy Volunteers-				
single dose:	X	2	1	BP19461 (Part 1) (supertherapeutic dose) MRA001JP
multiple dose:				
Patients-				
single dose:	X	1	1	LRO300
multiple dose:	X	3	3	MRA002JP MRA009JP LRO301
Dose proportionality -				

fasting / non-fasting single dose:	X	(2)		BP19461 (Part 1) MRA001JP
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1	1	MRA220JP (on CYP3A4 and CYP2C19) WP18663 (MTX, simvastatin) (Ongoing)
In-vitro:	X	1	1	ADM03-0155 (Effect of MRA and IL-6 on P450 expression levels in human hepatocytes)
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1	1	MRA221JP
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	4	4	WA17822 WA18063 WA18062 WA17824
Population Analyses -				
Data rich:				
Data sparse:	X	3 (4)	3	WA17822 WA18063 WA18062 WA17824 Study Report 1027775 (POP-PK, combined) Study Report 1027776 (POP-PK/PD) Study Report 1027777 (POP-PK/PD, combined)
II. Biopharmaceutics				
Absolute bioavailability:	X	1		WP18097 (sc vs. iv)
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
QT/QTc Evaluation	X	1		MRA004JP (ECG) BP19461 (Part 2) (Thorough QT, 10 and 20 mg/kg single dose) (Ongoing)
In Vitro Characterization of the Mechanism of Action of Tocilizumab	X			2 tests using human cell lines
Human Tissue Binding Studies	X			3 study reports

Immungenicity Study Report	X	1	1	1027841
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References	X			
Total Number of Studies		25	22	

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	X	Provide timeline on the submission of the study reports for the two on-going Clinical Pharmacology studies (WP18663 and BP19461 Part 2).
QBR questions (key issues to be considered)	• Have the single and multiple dose PK of tocilizumab been adequately characterized in healthy subjects and RA patients? • Is PK dose proportional? • What is the to-be-marketed formulation of tocilizumab? • Are various formulations of tocilizumab used throughout the clinical development adequately linked? • Have the analytical methods been adequately validated? • Do different analytical assays affect PK assessment? • What is the immunogencity of the product? • Have the antibody assays been adequately validated? • Does immunogenecity affect PK, PD, and efficacy/safety? • Is POP-PK analysis acceptable? • What are main covariates for PK? o Is there a need for dose adjustment? • Does exposure-response support the dose recommendation?	
Other Comments or information not included above		
Primary reviewer Signature and Date	Lei Zhang	
Secondary reviewer Signature and Date	Suresh Doddapaneni	

CC: BLA 125276, DAARP (Turner-Rinehardt), DCP2 (Zhang, Doddapaneni, Sahajwalla), CDR