CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276

MEDICAL REVIEW(S)

Clinical Review of Complete Response

Date	12-11-09
From	Sarah Okada, M.D. 12/17/09
Subject	Clinical Review
NDA/BLA # **Supplement#**	BLA 125276 Complete Response 0\64
Applicant	Hoffman La-Roche
Date of Submission	July 9, 2009
PDUFA Goal Date	January 9, 2010
Proprietary Name / **Established (USAN) names**	Actemra Tocilizumab
Dosage forms / Strength	Intravenous, 4 mg/kg or 8 mg/kg every 4 weeks
Proposed Indication(s)	1. Moderately to severely active Rheumatoid Arthritis
Recommended:	*Approval, with revisions to proposed labeling*

1. Introduction

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). 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. IL-6 is a pleiotropic cytokine that that has important roles in the regulation of the immune response, inflammation, and hematopoiesis. IL-6 is the primary driver of acute phase reactants, and hepatocytes express high levels of IL-6R. Elevated tissue and serum levels of IL-6 have been implicated in the pathophysiology of RA.

The original biologic license application (BLA) for tocilizumab in rheumatoid arthritis (RA) was submitted November 19, 2007, and received a complete response on September 17, 2008, due to deficiencies in the nonclinical program and on inspection of the manufacturing facilities. The clinical data submitted in the original BLA are derived from 5 randomized, double-blind, controlled trials of TCZ in 4211 RA patients with moderately to severely active disease. These data provided substantial evidence of the efficacy of TCZ for the treatment of RA. The safety data submitted, which included approximately 4700 patients and over 7900 patient-years of exposure in the global safety database, were consistent with the profile of an immunosuppressant, with an increased risk of serious infections. Likely related to mechanism of action, TCZ treatment also resulted in abnormalities of laboratory parameters, including decreased white blood cell count, increases in lipids, and liver enzyme elevations, although these were not associated with serious clinical adverse events in the controlled setting of the clinical trial experience. Malignancies, GI perforations, and demyelinating adverse events were observed in the clinical trials; however the relative risk and role of TCZ treatment in the development of these adverse events was not well-defined. Overall, the risk:benefit profile of TCZ in RA appeared to be favorable based on these clinical data.

A meeting of the Arthritis Advisory Committee was convened on July 29, 2008 to discuss the clinical data in the original tocilizumab BLA submission. The members of the committee concurred that efficacy was demonstrated in RA. They were uncertain whether the data clearly indicated a benefit of 8 mg/kg over the 4 mg/kg dose in patients with an inadequate response to DMARDs, as some members noted that the components of the ACR response criteria showed little difference between doses with the exception of effect on C-reactive protein (CRP) levels. The risk of serious infection was considered to be similar to that seen with commonly used agents in RA. GI perforation and demyelination adverse events were considered in light of their relative rarity, and the risks of these were not felt to outweigh the potential benefits observed with the product. The main area under discussion was the potential risk conferred by the elevation in LDL levels. Some members expressed great concern while other members were reassured by the lack of a signal for clinical cardiovascular events and by the potentially beneficial anti-inflammatory effects of tocilizumab on cardiovascular risk. The committee voted 10-to-1 in favor of approval.

If approved, TCZ would be the first IL-6 inhibitor approved for use in the United States. Roche's co-development partner, Chugai Pharmaceutical Co. Ltd., received approval in Japan in April 2005 for the use of TCZ in the treatment of multi-centric Castleman's Disease, a rare B-cell lymphoproliferative disorder. In April 2008, TCZ was approved in Japan for the treatment of adult RA, systemic juvenile idiopathic arthritis (SJIA), and polyarticular juvenile idiopathic arthritis (PJIA). As of May 15, 2009, TCZ has been approved for the treatment of moderately to severely active RA patients in the European Union (27 countries) and 15 other countries worldwide.

The clinical review of this complete response submission will focus on updated safety information submitted from the ongoing clinical trials and the post-marketing experience with TCZ in other countries, and whether there are data to confirm initial safety concerns or raise new ones. Review of these data will be done with special attention to the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, and whether the breadth and details of the REMS are appropriate to address the identified clinical concerns. The Applicant has also submitted revised proposed dosing, and a proposal for a cardiovascular outcomes assessment. No additional efficacy data were required or submitted for the complete response application. The reader is referred to the original clinical review of BLA 125276 for details of the efficacy and safety results submitted in the original BLA.

2. Background

The reasons for non-approval, as enumerated in the September 17, 2008 complete response letter were as follows:

1. Lack of peri-natal and post-natal developmental toxicology studies (feasible using either the monkey or the surrogate model)
2. Lack of fertility studies (not feasible in the primate, but feasible with the mouse homolog)
3. Proper name and dosage form should be presented consistently in all labeling and labels as "tocilizumab injection, solution, concentrate."

4. Carton and immediate container labels should include a statement that the product must be diluted before use.

5. Carton and immediate container labels need bolded statement annotating the requirement that patients receive a Medication Guide, as per 21 CFR 208.24(d).

6. A signed copy of the debarment certification must be submitted.

7. Explanation of why the financial disclosure information submitted on July 23, 2008 was not included with the original application.

8. Explanation of why Box 3 was checked on FDA form 3454 submitted July 23, 2008 for those investigators for whom financial information was not submitted, as this box is for studies sponsored by a firm or party other than the applicant.

9. Explanation of the due diligence steps taken to locate investigators for whom financial disclosure information was not obtained. For these investigators, information should be provided on reportable interests as can be ascertained from the Applicant's files.

10. Evidence of satisfactory resolution of the deficiencies identified on inspection of the Chugai Pharmaceutical manufacturing facility.

Also required with the complete response submission were a safety update and the submission of a REMS proposal which must contain a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for the submission of assessments. Items 1-10 above, and the requested REMS, have been adequately addressed in this complete response submission. For additional details of the response to items 1-2, refer to the Pharmacology/Toxicology reviews. The manufacturing deficiencies were addressed and submitted as previous amendments to the BLA, with previous Agency review which determined these deficiencies have been satisfactorily resolved.

Other issues which were not related to approvability but for which additional information was requested include:

A. Data to support the Applicant's position that, "The MR 16-1 antibody is also not an appropriate reagent to be used in long-term carcinogenicity studies, as this antibody is a rat monoclonal anti-mouse IL-6R antibody and is considered to be immunogenic in long-term in vivo studies in mice," and that this option is not viable for carcinogenicity assessment.

B. A summary table comparing the binding affinity of tocilizumab to both the human and monkey soluble and membrane-bound IL6R and a comparison of the functional potency of tocilizumab at the human and monkey IL-6R with references to the studies from which the data were obtained.

C. A reassessment of the benefit-risk balance of recommending only the 8 mg/kg dose, or consideration of a recommendation to start with a 4 mg/kg dose and increasing to the higher dose as needed and as tolerated.

D. More information on the proposed questionnaire for collecting adverse event data and the timeframe for following up on serious adverse events including infections. Also how information may be collected on pre-existing conditions or other factors that might predispose the patient to a serious adverse event, what treatments were tried, and the extent of those treatment successes.

E. Additional details regarding the proposed pharmacoepidemiology board.

F. Information on what will trigger a study in the registries or claims database.

G. Submission of protocols for the potential studies that use the registry and claims data.

Items A-G have also been addressed in this complete response submission. The applicant's dosing rationale and recommendations are discussed in Section 6 below. Items D-G will not be reviewed in detail in this memorandum, but will be referred for consultation to the Epidemiology division in the Office of Surveillance and Epidemiology (OSE). For items A and B, refer to the Pharmacology/Toxicology discipline reviews.

3. Brief Summary of Efficacy

As previously mentioned, the efficacy data submitted with the original BLA are derived from 5 double-blind, randomized, controlled trials enrolling a total of 4211 RA patients with moderately to severely active disease. Studies WA17822 and WA17823 evaluated tocilizumab (TCZ) at either 4 mg/kg or 8 mg/kg doses every 4 weeks vs. placebo + background methotrexate (MTX) in RA patients with inadequate response to methotrexate (MTX) or other DMARDs; Study WA18063 evaluated only the 8 mg/kg dose compared to placebo + background DMARDs. Study WA18062 assessed the safety and efficacy of tocilizumab at 4 mg/kg or 8 mg/kg vs. placebo + MTX in patients with a history of inadequate response to prior TNF inhibitor treatment. Study WA17824 assessed optimized MTX vs. TCZ 8 mg/kg monotherapy in methotrexate naïve RA patients.

Table 1: Proportion of ACR20/50/70 responders at Week 24 in the 5 Pivotal RA Studies

Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment (ITT Populations)					
Study	**Pbo + DMARD****	**TCZ 4mg/kg + DMARD****	**TCZ 8mg/kg + DMARD****	**p-value (4 mg/kg)**	**p-value (8 mg/kg)**
Patients with incomplete response to MTX or other DMARDs					
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
WA18063	(n=413)		(n=803)		
ACR20	**24**		**61**		**<0.0001**
ACR50	9		38		<0.0001
ACR70	3		20		<0.0001
Patients with incomplete response to prior TNF inhibitor treatment					
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

MTX naive/Early RA patients					
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 for primary analysis population

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 19 of WA17822 CSR, Tables 17 & 18 of WA17823 CSR, Tables 17 & 22 of WA17824 CSR
Tables 21 & 23 of WA18062 CSR, and Tables 17 & 20 of WA18063 CSR

As shown in Table 1 above, all five of these pivotal trials were consistent in demonstrating a treatment benefit in favor of tocilizumab with respect to the primary endpoint of ACR20 responses. For additional details of the study designs and efficacy results, the reader is referred to the clinical review for the original BLA 125276 November 19, 2007 submission.

4. Safety

Sources of safety data for the safety update in this complete response submission include updated cumulative safety data from the completed and ongoing RA pivotal trials and long-term extensions with a data cut-off of 6 Feb 09, encompassing a total of 4009 patients with 8580 patient-years exposure (most of which was to the 8 mg/kg every 4 week dose regimen). This population is annotated as the All-Exposure Population in the analyses that follow. This population was derived from the following studies:

- 4 completed 24-week controlled periods of WA17822, WA17824, WA18062, WA18063
- Double-blind transition phase of WA17824
- Completed two-year controlled phase of WA17823
- Ongoing open-label extension phase of WA17823

- Ongoing open-label long-term extension studies WA18695 and WA18696

Additional data on SAE and AE of interest (data cut-off of 25 Mar 09) were submitted from the following sources:

- Spontaneous reports
- [redacted] b(4)
- Compassionate use program
- ML21136 (RDBPC Phase 3b RA study)
- MA21573 (open-label Phase 3b RA study)
- WA19923 (MOA study on atherogenic markers in RA pts)
- WA18221/ext. (RCT in SJIA)
- ML21469: postmarketing study in Germany
- ML21753: postmarketing study in China
- ML21939 and ML21943: Japanese postmarketing surveillance studies in RA and PJIA
- ML21940: Japanese postmarketing surveillance study in SJIA
- ML19367: Japanese postmarketing surveillance study in Castleman's Disease

The applicant does not have information on the total number of patients who are being prescribed tocilizumab in the global marketplace since its approval in those countries. However, as of 12 Dec 08, patient exposure in Japan included for — adult RA patients, — PJIA patients, and — SJIA patients. In April 2009, the applicant distributed a total — vials in countries other than Japan, including — vials in Switzerland, — vials in the Netherlands, — vials in Austria, — vials in Germany, — vials in Denmark, — vials in Sweden, — vials in Finland, — vials in Peru, — vials in Ireland, and — vials in India. Tocilizumab vials come in 80 mg, 200 mg, and 400 mg total doses, so patients receiving 8 mg/kg and weighing more than 50 kg would have to receive at least two vials. Thus it is likely that — vials represents significantly fewer actual patients being dosed. b(4)

Where relevant, the safety tables that follow include previously submitted data from the pooled safety population from the 6-month controlled period of the 5 pivotal RA studies, and the previously submitted pooled safety data from the open-label extensions of these studies for comparison. As shown in Table 2 below, 1060 (26%) patients have withdrawn from the pivotal trials and long-term extensions through the February 6, 2009 data-cut-off date. Approximately half of the withdrawals were due to adverse events (AE), including 50 deaths. As might be expected, the number and percentage of patients discontinuing have accrued over time; most of this increase is attributable to patients discontinuing due to AE.

Table 2 Patient Disposition

Patient Disposition by Trial Treatment in the Tocilizumab RA Pivotal Studies and Long Term Extensions								
	6-months pooled safety population						Long term safety population	Updated All-exposure pop
	Placebo + DMARD* n (%)	MTX n (%)	TCZ 4mg/kg + MTX n (%)	TCZ 8mg/kg + DMARD* n (%)	TCZ 8mg/kg n (%)	All TCZ n (%)	Pooled TCZ n (%)	Pooled TCZ n (%)
Enrolled	1170	284	774	1582	288	2644	2562	4009
Completed	728 (62)	251 (88)	573 (74)	1364 (86)	262 (91)	2199 (83)	n/a	n/a
Entered escape	329 (28)	11 (4)	129 (17)	99 (6)	7 (2)	235 (9)	n/a	n/a
Withdrawals	126 (11)	22 (8)	78 (10)	121 (8)	19 (7)	218 (8)	377 (15)	1060 (26)
Discontinuation due to AEs								
AEs	35 (3)	10 (4)	42 (5)	75 (5)	5 (2)	122 (5)	158 (6)	493 (12)
Deaths	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)	50 (1.2)
Other withdrawals								
Insufficient treatment effect	51 (4)	3 (1)	11 (1)	8 (<1)	1 (<1)	20 (<1)	75 (3)	152 (4)
Protocol violation	5 (<1)	0	3 (<1)	3 (<1)	0	6 (<1)	2 (<1)	10 (<1)
Lost to follow-up	3 (<1)	1 (<1)	6 (<1)	3 (<1)	4 (1)	13 (<1)	20 (1)	58 (1)
Patient choice	26 (2)	7 (2)	15 (2)	27 (2)	6 (2)	48 (2)	84 (3)	223 (6)
Other	3 (<1)	0	1 (<1)	3 (<1)	0	4 (<1)	22 (1)	74 (2)

* Includes MTX
Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population; February 6, 2009 updated all-exposure pop
Adapted from Tables 8 and 11 of Module 2.7.4 Summary of Clinical Safety and tables stex11, ste11_wd and section 3.5 of 120 day safety update
stex11 and section 2.2 of July 2009 CR safety update

The number and types of adverse events causing discontinuation (DAE) are enumerated in Table 3 below. Abnormal laboratory values remain the most common cause of discontinuations (125 patients or 3%), with liver enzyme abnormalities being predominant among these. Infections and malignancies are the next most common etiologies resulting in discontinuation, each affecting approximately 2% of the study population. Overall, the pattern of adverse events causing discontinuation remains consistent with previously submitted data in the original BLA.

Table 3 Adverse Events Causing Discontinuation (DAE)

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, with Selected Preferred Terms

	6-months pooled safety population						Long term safety population	Updated All-Exposure 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	2562	4009
Total patients discontinuing due to AE	28 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)	543 (14)
Total number of AEs causing discont.	29	15	38	75	11	124	159	548
Investigations	**3 (<1)**	**4 (1)**	**15 (2)**	**37 (2)**	**2 (1)**	**54 (2)**	**40 (2)**	**125 (3)**
ALT or AST increased[a]	2	4	10	21	1	32	22	91 (2)
Neutrophils decreased[b]	-	-	3	6	1	10	8	28
Bilirubin increased[c]	-	-	2	7	-	9	4	16
Infections and Infestations	**7 (1)**	**1 (<1)**	**5 (1)**	**8 (<1)**	**1 (<1)**	**14 (<1)**	**24 (1)**	**99 (2)**
Pneumonia	2	-	2	1	1	4	7	18
Cellulitis	-	-	-	2	-	2	3	12
Neoplasms, benign/malig/NOS	**1 (<1)**	**3 (1)**	**1 (<1)**	**0**	**1 (<1)**	**2 (<1)**	**27 (1)**	**64 (2)**
Lung cancer[d]	-	1	-	-	-	-	7	13
Breast cancer	-	-	-	-	-	-	3	6
Gastric cancer	-	-	-	-	1	1	2	4
Gastrointestinal Disorders	**1 (<1)**	**5 (2)**	**1 (<1)**	**11 (1)**	**1 (<1)**	**13 (<1)**	**15 (1)**	**43 (1)**
GI perforation[e]	-	-	-	2	1	3	3	9
Skin and Subcutaneous Tissue	**1 (<1)**	**0**	**3 (<1)**	**6 (<1)**	**0**	**9 (<1)**	**9 (<1)**	**25 (1)**
Respiratory/Thoracic/Mediastinal	**1 (<1)**	**0**	**1 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**11 (<1)**	**21 (<1)**
Immune System Disorders	**0**	**1 (<1)**	**3 (<1)**	**3 (<1)**	**0**	**6 (<1)**	**3 (<1)**	**13 (<1)**
Anaphylactic reaction	-	-	2	1	-	3	2	9
Hypersensitivity	-	-	1	2	-	3	1	4
Nervous System Disorders	**2 (<1)**	**0**	**1 (<1)**	**3 (<1)**	**1 (<1)**	**5 (<1)**	**4 (<1)**	**22 (<1)**
Axonal neuropathy	-	-	-	-	-	-	2	2
Demyelination	-	-	-	-	-	-	1	-
Cardiac Disorders	**1 (<1)**	**0**	**0**	**1 (<1)**	**1 (<1)**	**2 (<1)**	**6 (<1)**	**18 (<1)**
Hepatobiliary Disorders	**0**	**0**	**0**	**1 (<1)**	**2 (<1)**	**3 (<1)**	**3 (<1)**	**11 (<1)**
Vascular Disorders	**2 (<1)**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**4 (<1)**	**13 (<1)**
Vasculitis[f]	-	-	-	-	-	-	3	7
Musculoskeletal and Connective Tissue	**6 (<1)**	**0**	**2 (<1)**	**0**	**1 (<1)**	**3 (<1)**	**2 (<1)**	**10 (<1)**
General Disorders/Admin. Site	**3 (<1)**	**0**	**1 (<1)**	**1 (<1)**	**1 (<1)**	**3 (<1)**	**1 (<1)**	**9 (<1)**
Infusion related reaction	1	-	-	1	1	2	-	4
Pregnancy/Puerperium/Perinatal	**1 (<1)**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**3 (<1)**	**15 (<1)**
Injury/Poison./Procedural Complic.	**0**	**0**	**1 (<1)**	**2 (<1)**	**0**	**3 (<1)**	**1 (<1)**	**11 (<1)**
Psychiatric Disorders	**0**	**1 (<1)**	**0**	**0**	**0**	**0**	**2 (<1)**	**6 (<1)**
Renal and Urinary Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**2 (<1)**	**3 (<1)**
Blood and Lymphatic System Disorders	**0**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**0**	**8 (<1)**
Reproductive System and Breast	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3 (<1)**
Surgical and Medical Procedures	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (<1)**
Metabolism and Nutrition Disorders	**0**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**0**	**4 (<1)**

* Includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population; February 6, 2009 for Complete Response Update

Multiple occurrences of the same AE in one individual are counted only once

Events on escape therapy are excluded

a) includes preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, liver function test abnormal

b) includes Blood and Lymphatic System Disorders preferred terms of neutropenia and leukopenia

c) includes Hepatobiliary Disorders preferred term of hyperbilirubinemia

d) includes preferred terms: lung adenocarcinoma, lung adenocarcinoma metastatic, lung neoplasm malignant, lung squamous cell carcinoma stage unspecified, non-small cell lung cancer, small cell lung cancer stage unspecified

e) includes preferred terms: diverticular perforation, gastrointestinal perforation, large intestine perforation

f) includes preferred terms: rheumatoid vasculitis, vasculitis, vasculitis necrotising, temporal arteritis

Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update, CR Update Table STae_rategp_wd_M

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Exposure-adjusted incidence of deaths, SAE, SIE and malignancies

Overall, the proportion and exposure-adjusted incidence of deaths, serious adverse events (SAE), serious infectious events (SIE), and malignancies has remained consistent with previously submitted safety data in the original BLA submission. As shown in Table 4 below, the cumulative number and proportion of patients who have died in the RA trials has increased (50 patients, 1.2% of total), however the exposure-adjusted incidence of death remains low at 0.6 deaths per 100 patient-years. This remains well below published background rates of death in RA patient cohorts, which are estimated at 2.4 to 2.5 deaths per 100 patient-years[1]. The exposure-adjusted incidence of malignancies is lower than that observed in the original BLA safety data, with 1.3 malignancies per 100 patient-years compared to 1.5 or 1.6 malignancies per 100 patient-years in the original BLA safety database. The exposure-adjusted incidence of SAE and SIE remains consistent with previously submitted safety data and observed exposure-adjusted rates of SAE and SIE for TNF inhibitors[2]: 16 SAE per 100 patient-years and 5.1 SIE per 100 patient-years in the extended exposure period of this submission.

Table 4 Exposure-Adjusted Incidence Rates of Deaths, SAE, SIE, and Malignancies

Exposure and Exposure Adjusted Incidence Rates for Deaths, SAEs, SIEs, and Malignancies in the Tocilizumab RA Pivotal Studies and Long-Term Extensions, with Updated Information from All-Exposure Population

	6-months pooled safety population						Long term safety population	Updated* All-exposure 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	2562	4009
Total patient-years exposure	462	123	321	685	126	1131	3685	8580
Deaths, n (%)	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)	50 (1.2)
Deaths per 100 pt-yrs	0.9	0.8	0	0.3	2.4	0.4	0.4	0.6
Malignancies, n (%)	7 (0.6)	3 (1)	5 (0.6)	10 (0.6)	2 (0.7)	17 (0.6)	60 (2.3)	109 (2.7)
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6	1.3
No. with ≥1 SAE, n (%)	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)	nr
Number of SAE	74	15	51	115	12	178	489	1404
SAEs per 100 pt-yrs	16	12	16	17	10	16	13	16
No. with ≥1 SIE, n (%)	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)	nr
Number of SIE	18	2	15	39	4	58	141	439
SIEs per 100 pt-yrs	3.9	1.6	4.7	5.7	3.2	5.1	3.8	5.1

*Clinical cut-off date of 6 Feb 09
nr=not reported

Deaths

The causes of death in the updated All-Exposure Population are consistent with what has been observed previously as well (Table 5 below). The most common causes of death remain malignancy, cardiovascular events, and infections. Overall, etiologies were those that might be expected to occur in the underlying study population of RA patients with multiple comorbidities and who are on immunosuppressive treatment.

[1] Gonzalez A, et al., "The Widening Mortality Gap Between Rheumatoid Arthritis Patients and the General Population." Arthritis & Rheum, November 2007, 56(11):3583-3587.

[2] Dixon WG et al., "Serious Infection Following Anti-Tumor Necrosis Factor Therapy in Patients with Rheumatoid Arthritis." Arthritis & Rheum, September 2007, 56(9):2896-2904.

Table 5 Deaths

Deaths in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Type and Trial Treatment								
	6-months pooled safety population						Long term safety pop Pooled TCZ	Updated All Exposure Pop
	Placebo + DMARD*	MTX	4mg/kg + MTX	8mg/kg + DMARD*	8mg/kg	All TCZ		
Enrolled	1170	284	774	1582	288	2644	2562	4009
Deaths	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)	50 (1.2)
Deaths per 100 pt-yrs	0.9	0.8	0	0.3	2.4	0.4	0.4	0.6
Malignancy	-	1	-	-	-	-	2	8
Cardiac ischemia/infarction	1	-	-	-	2	2	3	7
Infection/sepsis	1	-	-	-	-	-	4	5
Pneumonia	-	-	-	-	-	-	-	5
Unknown/cardiorespiratory arrest	-	-	-	-	-	-	1	5
CVA/subdural hematoma	-	-	-	1	-	1	-	4
Cardiac failure/cardiomyopathy	-	-	-	-	-	-	1	3
Pulmonary embolism	-	-	-	-	-	-	-	2
GI perforation	-	-	-	-	-	-	1	2
Post-procedural comp.	-	-	-	1	-	1	-	2
Suicide	-	-	-	-	-	-	2	2
Endocarditis	-	-	-	-	-	-	-	1
Multi-organ failure	-	-	-	-	-	-	-	1
Progressive Idiopathic Polyneuropathy	-	-	-	-	-	-	1	1
Acute renal failure	-	-	-	-	-	-	1	1
Dementia/infection	-	-	-	-	-	-	-	1
GI hemorrhage	-	-	-	-	1	1	-	-
Intestinal obstruction	1	-	-	-	-	-	-	-
Wegener's Granulomatosis	1	-	-	-	-	-	-	-

Adapted from Table 20 of Module 2.7.4 and Table 6 of 120 day safety update (cut-off date October 1, 2007), Table 3 of Roche 4-9-09 Submission, Data cut-off 3-25-09.
Updated all-exposure population data cut off 6 Feb 09, Table 6 of Complete Response Safety Update

Malignancies

The types of malignancies observed also mirrored what might be expected for the underlying study population, with the most common cancers being non-melanoma skin cancers, and the most common solid tumor cancers being lung, colorectal, and breast cancer in the All-Exposure Population (Table 6 below). Hematologic malignancies were uncommon, with 2 lymphoma and 2 leukemia diagnoses observed in these 4009 patients. Hematologic malignancies are not unexpected given that RA patients are known to have an increased relative risk of lymphoma and leukemias[3]. An assessment of the relative risk of specific types of malignancies compared to the general population follows (see Table 7 and referring text below).

[3] Anderson, et al., "Risks of myeloid malignancies in patients with autoimmune conditions," British Journal of Cancer 100, 822-828 (3 March 2009)

Table 6 Neoplasms and Malignancies

Neoplasms and Malignancies in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Type and Trial Treatment								
	6-months pooled safety population						Long term safety pop	Updated All-Exposure Population
	Placebo + DMARD[a]	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD[a]	TCZ 8mg/kg	All TCZ	Pooled TCZ	
Enrolled	1170	284	774	1582	288	2644	2562	4009
Total patients with ≥1 AE	7 (0.6)	3 (1.1)	5 (0.6)	10 (0.6)	2 (0.7)	17 (0.6)	65 (2.5)	101 (2.5)
Total neoplasms and malignancies	7	3	6	10	2	18	65	109[b]
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6	1.3
Solid Tumors								
Lung cancer	-	1	1	-	-	1	7	14
Colon or rectal cancer	1	1	-	1	-	1	2	6
Prostate cancer	1	-	-	-	-	-	2	6
Breast cancer, including in situ	1	-	-	-	-	-	4	5
Uterine cancer	-	-	-	1	-	1	1	5
Gastric cancer	-	-	-	-	1	1	2	4
Cervical cancer	-	-	1	-	-	1	3	4
Carcinoid tumor	-	-	-	-	-	-	-	3
Oropharyngeal cancer	-	-	-	-	-	-	-	3
Bladder neoplasm/cancer	-	-	-	-	-	-	-	2
Thyroid neoplasm/cancer	-	-	-	1	-	1	6	2
Sarcoma	-	-	-	-	-	-	-	2
Glioblastoma	-	-	-	-	-	-	1	1
Ovarian cancer	-	-	-	-	-	-	1	1
Melanoma	-	-	-	-	-	-	-	1
Pancreatic cancer	-	-	-	-	-	-	-	1
Renal cancer	-	-	-	-	-	-	-	1
Squamous cell carcinoma, unsp	-	-	-	1	-	1	3	1
Metastatic neoplasm	-	-	-	-	-	-	1	1
Lung neoplasm	1	-	1	2	-	3	9	-
Benign renal neoplasm	-	-	-	-	-	-	-	-
Bile duct cancer	-	-	-	-	-	-	-	-
Osteoma	-	-	-	-	-	-	-	-
Colon neoplasm	-	-	-	-	-	-	1	-
Adrenal neoplasm	-	-	-	-	-	-	1	-
Endometrial neoplasm	-	-	-	-	-	-	1	-
Meningeal neoplasm	-	-	-	1	-	1	1	-
Hepatic neoplasm	-	-	1	-	-	1	-	-
Non-melanoma skin CA								
Basal cell carcinoma	1	-	-	1	1	2	12	24
Squamous cell CA, skin	1	-	-	1	-	1	-	12
Skin cancer, NOS	-	-	1	-	-	1	-	2
Bowen's disease	-	-	1	1	-	2	3	-
Neoplasm, skin	-	-	-	-	-	-	1	-
Carcinoma in situ, skin	-	-	-	-	-	-	1	-
Dysplastic nevus syndrome	1	-	-	-	-	-	-	-
Hematologic/Lymphatic								
B-cell lymphoma	-	-	-	-	-	-	1	2
Acute Myeloid Leukemia	-	-	-	-	-	-	-	1
Chronic Lymphocytic Leukemia	-	-	-	-	-	-	-	1
Gammopathy	-	-	-	-	-	-	1	-
T cell lymphoma	-	1	-	-	-	-	-	-

a) Includes MTX b) Only malignancies listed
Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population; February 6, 2009 for complete response safety update
Adapted from source table STae11_mal of Module 2.7.4 Summary of Clinical Safety, Table 20 of 120 d safety update, Table STrate_6_mal_M and STae_py_6_mal_M of complete response safety update

When compared to the expected incidence of malignancy based on the National Cancer Institute's Surveillance Epidemiology End Results (SEER) general population database (see Table 7 below), the overall incidence of malignancy remains below expected, with both upper and lower limits of the 95% confidence interval remaining below one. For isolated organ classes, such as leukemia, cervical cancer and stomach cancer, the standardized incidence ratio

(SIR) is elevated. However, the relatively small numbers of the individual types of cancer observed thus far precludes definitive conclusions, and it should further be noted that the comparison is to the general population. RA patients are known to have an elevated risk of certain cancers, such as lymphoma and leukemia; thus expected rates of individual types of cancer in RA patients may differ from the general population represented by the SEER database. It should be noted that the SIR of lymphoma in the tocilizumab RA safety database is actually below that of the general population, which is particularly remarkable given the elevated background risk in RA patients. If this holds true, it may indicate that IL6 inhibition due to tocilizumab treatment may be protective against lymphomas.

Table 7 Standardized Incidence Ratio of Malignancies Compared to SEER Database

		95% Confidence Interval	
Organ Class	SIR[1]	Low	High
All Sites*	0.799	0.775	0.824
Brain and Other Nervous System	0.529	0.434	0.643
Cervix Uteri	2.616	2.206	3.103
Colon and Rectum	0.905	0.832	0.985
Corpus Uteri	0.908	0.719	1.146
Female Breast	0.287	0.171	0.479
Kidney and Renal Pelvis	0.454	0.373	0.552
Leukaemia	4.433	3.844	5.113
Lung	1.114	1.056	1.175
Non-Hodgkin Lymphoma	0.475	0.412	0.548
Oral Cavity and Pharynx	0.690	0.601	0.793
Ovary	0.339	0.263	0.435
Pancreas	0.340	0.280	0.414
Prostate	0.693	0.361	1.330
Stomach	3.747	3.326	4.220
Thyroid	1.047	0.906	1.210
Urinary Bladder	0.362	0.314	0.416

Source: Complete Response Safety Update, p. 1460
*All Sites values include 6 single malignancies not included in the listed specific organ classes above

Serious Adverse Events

The types of SAE observed in the All-Exposure Population are summarized by system-organ-class (SOC) in Table 1Table 8 below. Infections were by far the most common SAE, affecting 9% of patients. Gastrointestinal Disorders, Injuries, and Neoplasms SOC were the next most common, each affecting 3% of study patients.

Table 8 Serious Adverse Events

Serious Adverse Events (SAE) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment and SOC								
	6-months pooled safety population						Long term safety pop	Updated All-Exposure 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	2562	4009
Total patients with ≥ 1 SAE	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)	934 (23)
Total number of SAEs	74	15	51	115	12	178	489	1404
SAEs per 100 pt-yrs	16	12	16	17	10	16	13	16
Infections and Infestations	**17 (1)**	**2 (1)**	**13 (2)**	**38 (2)**	**4 (1)**	**55 (2)**	**133 (5)**	**355 (9)**
Gastrointestinal Disorders	**6 (<1)**	**1 (<1)**	**3 (<1)**	**14 (1)**	**2 (1)**	**19 (1)**	**44 (2)**	**106 (3)**
Injury, Poison., Procedural Complic.	**4 (<1)**	**3 (1)**	**4 (<1)**	**14 (1)**	**1 (<1)**	**19 (1)**	**50 (2)**	**117 (3)**
Neoplasms, benign/malignant/NOS	**4 (<1)**	**3 (1)**	**3 (<1)**	**2 (<1)**	**1 (<1)**	**6 (<1)**	**38 (1)**	**105 (3)**
Cardiac Disorders	**5 (<1)**	**0**	**1 (<1)**	**7 (<1)**	**2 (1)**	**10 (<1)**	**22 (1)**	**84 (2)**
Musculoskeletal/Connective Tissue	**9 (1)**	**1 (<1)**	**3 (<1)**	**5 (<1)**	**0**	**8 (<1)**	**29 (1)**	**79 (2)**
Nervous System Disorders	**3 (<1)**	**0**	**6 (1)**	**9 (1)**	**1 (<1)**	**16 (1)**	**17 (1)**	**74 (2)**
Respiratory/Thoracic/Mediastinal	**3 (<1)**	**1 (<1)**	**2 (<1)**	**4 (<1)**	**0**	**6 (<1)**	**15 (1)**	**54 (1)**
Vascular Disorders	**4 (<1)**	**1 (<1)**	**2 (<1)**	**2 (<1)**	**0**	**4 (<1)**	**15 (1)**	**50 (1)**
General and Admin site	**4 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**0**	**2 (<1)**	**6 (<1)**	**28 (1)**
Blood and Lymphatic	**2 (<1)**	**0**	**4 (<1)**	**2 (<1)**	**0**	**6 (<1)**	**4 (<1)**	**24 (1)**
Renal/Urinary	**1 (<1)**	**0**	**1 (<1)**	**3 (<1)**	**0**	**4 (<1)**	**8 (<1)**	**23 (1)**
Hepatobiliary	**1 (<1)**	**0**	**0**	**2 (<1)**	**1 (<1)**	**3 (<1)**	**6 (<1)**	**23 (1)**
Reproductive/Breast	**1 (<1)**	**0**	**1 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**6 (<1)**	**21 (1)**
Psychiatric Disorders	**1 (<1)**	**1 (<1)**	**2 (<1)**	**1 (<1)**	**0**	**3 (<1)**	**4 (<1)**	**21 (1)**
Skin and Subcutaneous	**1 (<1)**	**0**	**0**	**2 (<1)**	**0**	**2 (<1)**	**2 (<1)**	**15 (<1)**
Pregnancy, Puerperium, Prenatal	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**13 (<1)**
Immune System	**0**	**0**	**2 (<1)**	**0**	**0**	**2 (<1)**	**0**	**10 (<1)**
Eye Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**9 (<1)**
Metabolism/Nutrition	**2 (<1)**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**0**	**8 (<1)**
Investigations	**0**	**0**	**0**	**1 (<1)**	**0**	**1 (<1)**	**-**	**5 (<1)**
Ear and Labyrinth	**2 (<1)**	**0**	**0**	**0**	**0**	**0**	**2 (<1)**	**5 (<1)**
Endocrine	**0**	**0**	**0**	**1 (<1)**	**0**	**1 (<1)**	**1 (<1)**	**4 (<1)**
Congenital, Familial, Genetic	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2 (<1)**
Surgical/Medical Procedures	**0**	**0**	**1 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**0**	**2 (<1)**
Social Circumstances	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (<1)**

* Includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population, February 6, 2009 for updated all-exposure population

Adapted from Table 24 of Module 2.7.4 Summary of Clinical Safety and Table stae11_sl of 120 d safety update, Table Stae_rategp_np_s1M and Strate_6_ae_s1M of Complete Response Safety Update

Serious Infections

By far the most common serious infections observed in the All-Exposure Population were pneumonias, followed by cellulitis, various soft tissue and intra-abdominal abscesses, gastroenteritis, and infections resulting in sepsis (Table 9 below). Opportunistic infections and serious viral infections were also observed, including 9 cases of TB, 10 cases of herpes zoster exacerbations, 2 cases of atypical mycobacterial infections, a case of Pneumocystis Jiroveci pneumonia, a case of cryptococcal pneumonia, and a case of fungal sinusitis. These infections suggest that IL6 inhibition related to tocilizumab treatment results in significant immunosuppression. These types of infections have been noted with other immunosuppressive treatments, including corticosteroids and TNF inhibitors.

Table 9 Serious Infectious Events

Selected Serious Infectious Events (SIE) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment

	6-months pooled safety population						Long term safety pop	Updated All-Exposure 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	2562	4009
Total patients with ≥ 1 SIE	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)	360 (9)
Total number of SIEs	18	2	15	39	4	58	141	439
SIEs per 100 pt-years	3.9	1.6	4.7	5.7	3.2	5.1	3.8	5.1
Pneumonia/complicated pneumonia	4	1	5	9	2	16	35	103
Cellulitis	1	-	-	11	-	11	21	63
Abscess	4	-	-	2	-	2	9	23
Gastroenteritis/Diarrhea	-	-	3	-	-	3	8	22
Sepsis	1	1	2	1	-	3	4	21
Urinary tract infection/pyelo	5	-	1	3	-	4	5	19
Diverticulitis/appendicitis	-	-	-	-	-	-	6	18
Bacterial arthritis/tenosynovitis	-	-	-	2	-	2	3	16
Post procedural/wound infection	-	-	-	-	-	-	-	16
Bronchitis								12
Respiratory tract infection	1	-	2	2	-	4	7	11
Herpes zoster	-	-	-	5	-	5	8	10
M. TB, pulm & extra pulm	-	-	-	-	-	-	2	9
Infection NOS	-	-	-	-	-	-	-	8
Osteomyelitis/intervertebral discitis	2	-	1	-	-	1	3	6
Varicella	-	-	-	-	-	-	-	4
Atypical mycobacterial	-	-	-	-	-	-	1	2
Candidiasis/candida osteomyelitis	-	-	-	-	-	-	-	2
Pneumocystis Jiroveci pneumonia	-	-	1	-	-	1	-	1
Meningitis	-	-	-	-	-	-	-	1
Herpes encephalitis	-	-	-	-	-	-	-	1
Pneumonia, cryptococcal	-	-	-	-	-	-	-	1
Sinusitis, fungal	-	-	-	-	-	-	-	1

* Includes MTX

Data cut-off April 20, 2007; October 1, 2007 for long-term safety population, February 6, 2009 for complete response safety update

Adapted from Table 27 of Module 2.7.4 Summary of Clinical Safety and Table 9 of 120 d safety update, Table Strate_6_ae_s_infec_M and Stae_rategp_hlgt_inf_sM from complete response safety update

Laboratory Abnormalities

Hepatobiliary Laboratory Abnormalities

Consistent with its mechanism of action (IL6 inhibition via binding of cell surface IL6 receptors), tocilizumab treatment is associated with reversible elevation in hepatobiliary parameters. Hepatocytes express high levels of IL6 receptor, and IL6 drives hepatic production of acute phase reactants. As discussed in the original BLA, although the mechanism of action of tocilizumab-mediated hepatobiliary laboratory abnormalities has not been elucidated, there are plausible mechanisms by which these might occur. First, IL6 appears to have a hepatoprotective effect on various forms of liver injury and promotes hepatocyte regeneration. Therefore inhibition could lead to increased hepatocyte susceptibility to hepatotoxic insults. Less likely, since tocilizumab does not induce significant effector function, is the possibility that tocilizumab binding on hepatocyte surface IL6 receptors could result in some complement-mediated cytotoxicity, or antibody-dependent cellular cytotoxicity.

Thus far, these abnormalities do not appear to be correlated with clinical hepatotoxicity, and are reversible with discontinuation of treatment. As shown in Table 10 below, approximately 50% of patients treated with tocilizumab experience elevations in AST or ALT up to 3 times

the upper limit of normal (ULN). A small percentage of patients experienced elevations from 3 to 5 x ULN, and yet smaller proportions experienced elevations from 5 to 8 x ULN.

Table 10 Hepatobiliary Laboratory Worst Values

Hepatobiliary Worst Values in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
		6-months pooled safety population					Long term safety pop	Updated
	range	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	Pooled TCZ	All-Exposure Population
Enrolled		1170	284	774	1582	288	2562	4009
Pts discontinued for abnl		**2 (<1)**	**4 (1)**	**12 (2)**	**28 (2)**	**1 (<1)**	**26 (1)**	**91 (2)**
Dose mod/interrupted		**8 (1)**	**24 (8)**	**19 (2)**	**37 (2)**	**22 (8)**	**151 (6)**	**315 (8)**
AST (U/L)								
>ULN to 3 x ULN	41-120	194 (17)	74 (26)	264 (34)	646 (41)	64 (22)	1176 (46)	1961/3812 (51)
>3 x ULN to 5 x ULN	121-200	3 (0.3)	5 (2)	8 (1)	29 (2)	1 (0.3)	53 (2)	98/3812 (3)
>5 x ULN to 8 x ULN	201-320	-	1 (0.4)	1 (0.1)	1 (0.1)	1 (0.3)	7 (0.3)	22/3812 (0.6)
>8 x ULN	>320	1 (0.1)	-	-	2 (0.1)	1 (0.3)	2 (0.1)	
ALT (U/L)								
>ULN to 3 x ULN	56-165	270 (23)	95 (33)	349 (45)	763 (48)	105 (36)	1370 (53)	2112/3689 (57)
>3 x ULN to 5 x ULN	166-275	15 (1)	11 (4)	36 (5)	80 (5)	4 (1)	170 (7)	267/3689 (7)
>5 x ULN to 8 x ULN	276-440	1 (0.1)	2 (0.7)	10 (1)	21 (1)	1 (0.3)	20 (0.8)	83/3689 (2)
>8 x ULN	>440	2 (0.2)	1 (0.4)	-	2 (0.1)	1 (0.3)	7 (0.3)	
Total Bilirubin (umol/L)								
>ULN to 3 x ULN	18-51	9 (0.8)	2 (0.7)	46 (6)	141 (9)	23 (8)	308 (12)	573 (14)
>3 x ULN to 5 x ULN	52-85	1 (0.1)	-	-	1 (0.1)	-	-	2 (0.04)
>5 x ULN to 8 x ULN	86-136	-	-	-	-	-	-	
>8 x ULN	>136	-	-	1 (0.1)	-	-	-	

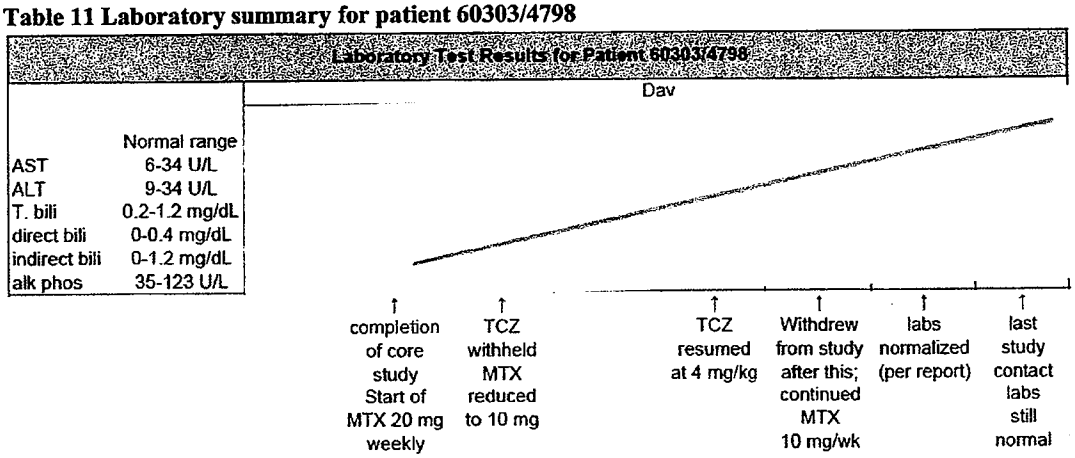
*Includes MTX

Source: Tables 40 and 41, STae_rategp_wd_M and STae_rategp_mod_M of Complete Response Safety Update

To date, five patients in the Roche clinical development program have had a > 3 x ULN accompanied by elevated total bilirubin > 2 x ULN. Each of the five cases was adjudicated by hepatology consultant [redacted] and one case (patient 60303/4798) was also reviewed by [redacted] None of these cases meets true Hy's Criteria, in that in each case there was either evidence of biliary obstruction/Gilbert's syndrome, or in one case, temporally related exposure to hepatotoxic medications (antituberculous medications). b(4)

a) Patient 60303/4798. This patient is a 57 year old female with a 9-year history of RA, who received TCZ 8 mg/kg monotherapy in Study WA17824, and received TCZ 8 mg/kg in Study WA18696. The patient's treatment and labs over time are shown in Table 11, below. This was the case identified during review of the original submission for BLA 125276 and determined to be consistent with Gilbert's Syndrome and level 1 drug-induced liver injury; both MTX and TCZ likely contributed to the laboratory elevations. This patient was asymptomatic, and liver enzyme abnormalities resolved with discontinuation of TCZ treatment.

Table 11 Laboratory summary for patient 60303/4798



Source: narrative and Table 3, 4-9-09 submission

b(4)

b) Patient 50982/7194. This patient is a 31 year old female patient with a 9-year history of RA, who received TCZ 8 mg/kg + DMARD in Study WA 18063). The patient had a one-year history of cholelithiasis detected incidentally by ultrasound. On study day 104, while hospitalized for gallstones, her AST was 158 U/L (4.6 x ULN) and total bilirubin was 6.6 mg/dL (5.5 x ULN). On study day 112, she underwent cholecystectomy and AST and total bilirubin normalized.

c) Patient 50869/6068. This is a 70-year old female patient with a 6-year history of RA, who also had a history of cholecystectomy in 1988 and had been taking stable MTX at 20 mg/week since 2003. During the core study WA18063, the patient was randomized to placebo + DMARD and had normal liver enzymes. She enrolled in extension study WA18696 and received TCZ 8 mg/kg. During the first 24 weeks of the extension, the patient had occasional ALT and/or AST elevations not exceeding 3 x ULN, with normal bilirubin and alkaline phosphatase levels. These were managed by discontinuation of her MTX and by either withholding the TCZ dose or on one occasion (Extension Week 4) lowering to 4 mg/kg. From week 28 onward, the TCZ dose remained steady at 8 mg/kg. Starting on Study day 574, the patient complained of increasing joint pain, intermittent epistaxis, low back pain and dyspnea on exertion. Labs associated with her subsequent course are shown in Table 12. The applicant's hepatology consultants have adjudicated this as a case of largely cholestatic liver injury that might have been due to a retained common duct stone (not confirmed). However, they also conclude that it is not possible to exclude TCZ treatment as a cause. This case also does not meet Hy's criteria in that there was likely a prominent cholestatic component (based on alkaline phosphatase elevation). Although it would be unusual for a patient to have tolerated well over a year of treatment, the patient's liver and hematologic abnormalities have been observed with TCZ treatment, and the patient did not have other symptoms to suggest alternative etiologies (such as viral infection). The patient's abnormalities were reported as resolved after discontinuation of TCZ treatment, again implicating TCZ as a causative factor.

Table 12: Laboratory summary for patient 50869/6068

Laboratory Test Results for Patient 50869/6068

	Normal range	Extension Study Day 574	589	597
AST	6-34 U/L			
ALT	9-34 U/L			
T. bili	0.2-1.2 mg/dL			
alk phos	35-123 U/L			
WBC				
hemoglobin	11.8-14.8 g/L			
PLTs	130-394 x 10^3/uL			

nr=not reported
wnl=within normal limits

↑ epistaxis jt pain back pain DOE

↑ hosp for severe epistaxis and blood transfusion d/cd study

Source: narrative 4-9-09 submission

b(4)

d) Patient 46721/2424. This is a 29-year-old male patient with RA of 6 months duration who was randomized to TCZ 4 mg/kg + MTX in Study WA 17823 and received 4 doses of TCZ 4 mg/kg and then switched to TCZ 8 mg/kg for the remaining time on study. At baseline the patient had mild elevation of total bilirubin (mostly indirect, see Table 13 below), and throughout most of his course his bilirubin levels fluctuated between normal and slightly above normal. However on Study Day 505, the patient had increased ALT and bilirubin, as shown in Table 13. The patient's MTX dose was reduced from 10 mg/weekly to 5 mg/weekly, but he was discontinued from further study treatment 3 days later. By Study Day 533, his ALT had normalized, and bilirubin levels normalized by Study Day 564. The applicant's hepatology consultants have adjudicated this case as a likely case of Gilbert's syndrome, based on the predominance of indirect bilirubin levels. They also state that the patient's intermittent mild ALT elevations may have been related to TCZ treatment. I concur with both these conclusions.

Table 13: laboratory summary for patient 46721/2424

Laboratory Test Results for Patient 46721/2424

Day

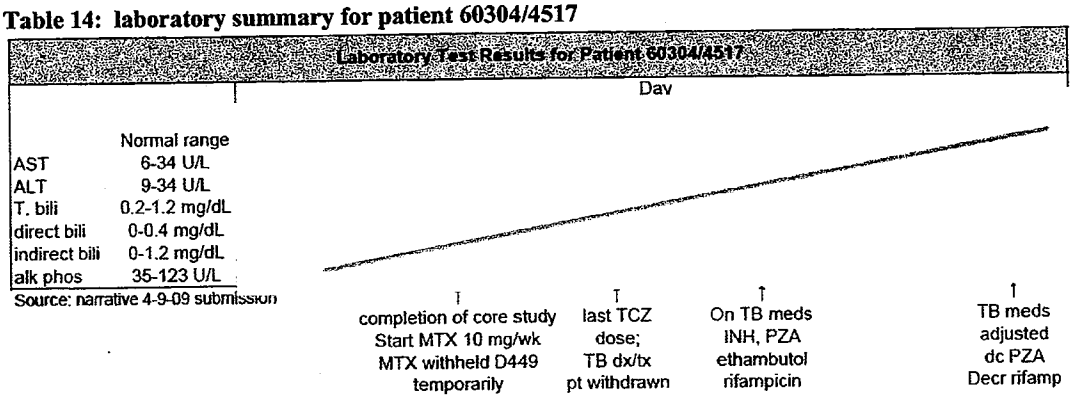
Source: narrative
4-9-09 submission
nr=not reported

↑ MTX reduced to 5 mg/wk pt d/cd MTX and from study on Day 508

b(4)

e) Patient 60304/4517. This patient is a 26 year-old-woman with RA of 2-years duration who was randomized to TCZ 8 mg/kg monotherapy in Study WA17824, then received TCZ 8 mg/kg in extension Study WA18696. During the core study, the patient had mild intermittent ALT elevations which worsened with the start of MTX treatment in the long-term extension. However, the patient's most significant hepatobiliary laboratory abnormalities did not occur until the discontinuation of TCZ and the start of her anti-tuberculosis medication regimen (See Table 14 below). The applicant's consultants have adjudicated this as possible TCZ-related mild enzyme elevations but with anti-tuberculosis medications being responsible for the most significant abnormalities. This was supported by resolution of liver enzyme abnormalities after pyrazinamide (PZA) was discontinued and rifampin dose was reduced. I concur with the applicant's conclusions in this case.

Table 14: laboratory summary for patient 60304/4517



b(4)

Liver Biopsy Results in Patients with Persistent Liver Enzyme Elevations

Although the study protocols did not mandate liver biopsies, principal investigators were instructed that following withdrawal due to elevated liver function tests, patients were to have repeat testing until the tests were within the normal range. If the patient's liver function tests did not return to normal within 6 months (or sooner, if deemed necessary by the investigator), a liver ultrasound and biopsy were recommended. Thus far, in the Roche TCZ clinical development program, liver biopsies have been done on 16 patients. As of the time of this submission, 12 of 16 have been reviewed by the local pathology site and an independent central pathology reader, [redacted] The remaining 4 biopsy slide sets are pending release of samples by the local pathology laboratories.

b(4)

Roche has provided narratives for all 16 patients, side-by-side biopsy results as reported by the local pathologist and central reader for 12 patients, and the preliminary results from the locally read pathology evaluation for 3 of the 4 remaining patients (1 report had not yet been received by Roche). To summarize, 12 of 15 pathology reports showed varying degrees of steatohepatitis, one patient had features consistent with an abscess, and two patients had normal biopsy findings. Findings of advanced fibrosis were noted in 5 patients, all of whom had potentially confounding conditions (obesity/diabetes, autoimmune hepatitis, chronic alcohol use).

Overall the patients who received biopsy had multiple confounding variables, to include concomitant MTX use and comorbidities, and biopsy results were nonspecific; therefore no definitive conclusions can be drawn from these data. However, there were also no findings to definitively implicate drug-induced liver injury, and more specifically, tocilizumab-mediated liver injury.

Clinical Hepatotoxicity Events

To thoroughly identify clinical hepatotoxicity events in TCZ-treated patients, the applicant utilized the following two Standardized MedDRA Queries (SMQs): hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions and hepatitis, non-infectious, as well as the hepatobiliary disorder and investigations system-organ-classes (SOCs). A total of 57 hepatotoxicity events were reported in 56 patients in the Roche RA clinical development program to date, as identified by the SMQs (Table 15). Review of the submitted narratives revealed the vast majority of these events were hepatic steatosis in patients who were actually asymptomatic but identified by laboratory and radiographic abnormalities. Likewise most of the other listed AEs of were asymptomatic patients with laboratory and radiographic abnormalities.

Table 15 all hepatotoxicity events in Roche RA program identified by smq search

Body System/ Adverse Event	ALL TCZ N = 4009 No. (%)
ALL BODY SYSTEMS	
Total Pts with at Least one AE	56 (1.4)
Total Number of AEs	57
HEPATOBILIARY DISORDERS	
Total Pts With at Least one AE	56 (1.4)
HEPATIC STEATOSIS	42 (1.0)
HEPATOTOXICITY	3 (<0.1)
HEPATIC FIBROSIS	2 (<0.1)
HEPATIC LESION	2 (<0.1)
LIVER DISORDER	2 (<0.1)
AUTOIMMUNE HEPATITIS	1 (<0.1)
CYTOLYTIC HEPATITIS	1 (<0.1)
GRANULOMATOUS LIVER DISEASE	1 (<0.1)
HEPATITIS	1 (<0.1)
HEPATITIS TOXIC	1 (<0.1)
ISCHAEMIC HEPATITIS	1 (<0.1)
Total Number of AEs	57

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
This output was run on live data received 30th March 2009 rather than a locked data base
AE11 02APR2009:15:58:36

Source: Sponsor Table 6, 4-9-09 IND submission, data cutoff 30 March 2009

Serious hepatotoxicity adverse events

Three serious adverse events were identified on SMQ search:

1. Autoimmune hepatitis (patient 46690/2794) was reported in a 59-year old female with a pre-existing history of hepatic enzyme elevation and autoimmune hepatitis treated with prednisone. At baseline her AST was 59 U/L (reference 9-34) and her ALT was 51 U/L (reference 6-34). Over the course of the study the ALT/AST generally remained between 1.5x and 3x ULN, with occasional episodes >3x ULN. A liver biopsy was performed for persistent transaminase elevations. The presence of lymphoid aggregates on the biopsy supported the diagnosis of autoimmune hepatitis and the patient was discontinued from the study.

2. Hepatic steatosis (patient 51146/4375): This patient was diagnosed with cytolytic hepatitis based on persistent elevation of ALT/AST between 1x and 3x ULN. On study day 720, a liver biopsy was performed which demonstrated hepatic steatosis. This was reported as a serious adverse event. The transaminases returned to within the normal range following discontinuation of treatment with TCZ.

3. Ischemic hepatitis (patient 51181/4890) was reported in a 62-year old female taking losartan and nicardipine for hypertension. Approximately 15 hours post-infusion she had a hypotensive episode (blood pressure 80/40) and was hospitalized. AST and ALT were elevated at 1248 and 747 U/L, respectively, on admission. The patient was diagnosed with drug hypersensitivity and treated with fluid resuscitation and prednisolone. Liver function tests returned to normal following treatment. The patient was withdrawn from the study due to the event of drug hypersensitivity.

Overall, the data reported in this submission are consistent with the data reported in the original submission for BLA 125276. Tocilizumab treatment appears to be associated with liver enzyme abnormalities but does not appear to yet have been directly associated with severe clinical hepatotoxicity.

Hematologic Laboratory Abnormalities

IL6 is an essential hematopoietic growth factor; therefore its inhibition can result in reduction in white blood cells and platelets. Up to 20% of patients treated with tocilizumab experience Grade 1 or Grade 2 neutropenia, however few experience more severe neutropenia (See Table 16 below). In the clinical trial experience thus far, this neutropenia has been associated with few clinical adverse events: 1 case of atypical mycobacterial infection occurring after 2 months of low absolute lymphocyte count associated with TCZ treatment, 1 case of sepsis associated with a bile duct stone in a patient with low WBC (400/mm^3) in Japanese postmarketing surveillance, and 1 case of empyema associated with Grade 3 neutropenia. Neutropenia is reversible with discontinuation of treatment.

Table 16 Neutropenia Worst Values

Neutropenia (Worst Values) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions							
	6-months pooled safety population					Long term safety pop Pooled TCZ	Updated All-Exposure Population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg		
Enrolled	1170	284	774	1582	288	2562	4009
Pts discontinued for abnl	-	-	3 (<1)	7 (<1)	1 (<1)	10 (<1)	28 (<1)
Dose mod/interrupted	-	1 (<1)	3 (<1)	9 (1)	7 (2)	74 (3)	129 (3)
Grade 1 (1500 to LLN/mm^3)	30 (3%)	22 (8%)	88 (11%)	298 (19%)	51 (18%)	498 (19%)	813 (20%)
Grade 2 (1000 to 1500/mm^3)	10 (<1%)	6 (2%)	53 (7%)	179 (11%)	30 (10%)	371 (14%)	642 (16%)
Grade 3 (500-1000/mm^3)	-	1 (<1%)	9 (1%)	48 (3%)	9 (3%)	91 (4%)	165 (4%)
Grade 4 (<500/mm^3)	-	-	3 (<1%)	5 (<1%)	-	6 (<1%)	29 (<1%)

*Includes MTX
Worst values within a time window per patient are summarized
Source: Roche AAC presentation and Tables 18 and STae_rategp_mod_M and STae_rategp_wd_M of Complete Response Safety Update

Table 17 Thrombocytopenia Worst Values

Thrombocytopenia (Worst Values) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions							
	6-months pooled safety population					Long term safety pop Pooled TCZ	Updated All-Exposure Population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg		
Enrolled	1170	284	774	1582	288	2562	4009
Pts discontinued for abnl							8 (0.2)
Dose mod/interrupted							14 (0.3)
Grade 1 (75,000 to LLN/mm^3)	15 (1%)	2 (<1%)	42 (5%)	136 (9%)	26 (9%)	278 (11%)	560 (14%)
Grade 2 (50,000 to 75,000/mm^3)	1 (<1%)	1 (<1%)	3 (<1%)	4 (<1%)	1 (<1%)	19 (<1%)	30 (<1%)
Grade 3 (25,000-50,000/mm^3)	1 (<1%)	-	-	3 (<%)	-	8 (<1%)	13 (<1%)
Grade 4 (<25,000/mm^3)	1 (<1%)	-	3 (<1%)	2 (<1%)	-	6 (<1%)	19 (<1%)

*Includes MTX
Worst values within a time window per patient are summarized
Source: Roche AAC presentation and Tables 14 and STae_rategp_mod_M and STae_rategp_wd_M of Complete Response Safety Update

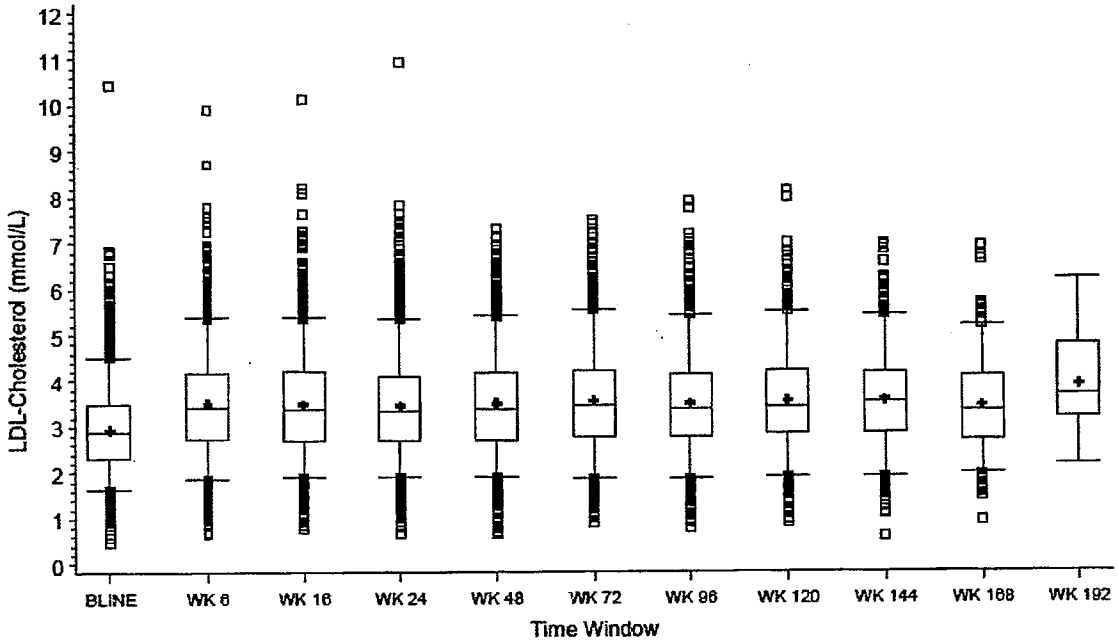
Similarly, mild thrombocytopenia associated with tocilizumab treatment is not uncommon (see Table 17 above), but has been associated with very few clinical adverse events and is reversible with discontinuation of treatment. Four bleeding events in patients with Grade 3 or 4 thrombocytopenia have occurred (epistaxis-2, hemoptysis-1, hemorrhagic stomatitis-1).

Lipid parameter abnormalities

TCZ treatment has been associated with an increase in all lipid parameters—average increases of 30 mg/dl in total cholesterol, 20 mg/dl in LDL, 5 mg/dl in HDL, and 30-40 mg/dl in triglycerides. As shown in Figure 1 below, LDL increases took place by Week 6 and did not increase further with successive TCZ treatment over time.

Figure 1 Box Plot of LDL-Cholesterol (mmol/L) Over Time-All Exposure Population

SGlb_box_lip_ldl_M Box Plot of LDL-Cholesterol (mmol/L) Over Time - All Exposure Population (Safety Population)



Only worst values used if more than one fasted assessment was present for a visit. If the fasting information was missing (or not YES) the assessment was assumed to be non-fasted. Excludes local analysis where central analysis on same day. Lower whisker,lower limit of box,middle line,upper limit of box,upper whisker and + symbol represent the 5th percentile, first quartile,median,third quartile,95th percentile and mean values respectively.

Program : $PROD/cd11935l/p11935f/SGlb_box_lip.sas
Output : $PROD/cd11935l/p11935f/reports/SGlb_box_lip_ldl_M.cgm
20APR2009 7:37

Note: mmol/L = 38.6 mg/dL

Source: Figure 5 from complete response safety update

The number and proportion of patients shifting between ATPIII LDL categories from baseline to last observation are summarized in Table 18 below. Nine hundred twenty four patients (23%) shifted from LDL below 130 mg/dl to LDL above 130 mg/dl.

Table 18 Lipid Parameters: Change from Baseline to Last Observation-All Exposure Population

Laboratory Test - LDL-Cholesterol

	LAST VALUE <100	100<=Y<130	130<=Y<160	>=160	MISSING
BASELINE					
ALL TCZ (N=4009)					
<100	554 (13.8%)	438 (10.9%)	204 (5.1%)	81 (2.0%)	10 (<1%)
100<=Y<130	170 (4.2%)	430 (10.7%)	388 (9.7%)	281 (7.0%)	16 (<1%)
130<=Y<160	50 (1.2%)	109 (2.7%)	223 (5.6%)	315 (7.9%)	7 (<1%)
>=160	14 (<1%)	41 (1.0%)	85 (2.1%)	210 (5.2%)	7 (<1%)
MISSING	85 (2.1%)	85 (2.1%)	90 (2.2%)	85 (2.1%)	31 (<1%)

LDL-Chol threshold: < 100 mg/dl; 100<= y <130 mg/dl; 130<= y <160 mg/dl; >= 160 mg/dl
Excluding local analysis where central analysis is available on same day.
This output only contains fasted lipids.
Program : $PROD/cdl19351/pl1935f/STIbshift_bl_lip.sas
Output : $PROD/cdl19351/pl1935f/reports/STIbshift_bl_lipid_M.r18 20APR2009 7:56
PDRD

Source: Table 37 of Complete Response Safety Update

The applicant also provided data to support the effectiveness of lipid-lowering agents to manage tocilizumab-related increases in lipid parameters (Figure 6 of the Complete Response Safety Update, data not shown). In 313 patients who experienced TCZ-related increases and began lipid-lowering agents during the study, LDL values returned to below baseline levels.

Thus far, there continues to be no safety signal with respect to lipid parameter elevations resulting in cardiovascular adverse events. As mentioned in the original BLA review, the background rate of myocardial infarction (MI) events in RA has been reported to be 0.5 to 0.8 events per 100 patient-years[4]. In the original BLA, there were 15 cardiovascular events in 4158 patient-years exposure, which equates to 0.4 events per 100 pt-yrs. In the updated All-Exposure population, there have been a cumulative 24 events in 8580 patient-years exposure, or 0.3 events per 100 patient-years. Thus, over time, the rate of MI has remained below published background rates for RA patients and has not increased.

Similarly, the rate of cerebrovascular accidents (CVA) has remained within published background rates in RA patients and has not increased over time. Reported background rates for RA patients range from 0.1 to 0.8 events per 100 patient-years[5]. In the original BLA, there were 9 CVA events in 4158 patient-years exposure, or 0.2 events per 100 patient-years. In the updated All-Exposure population, there have been a cumulative 18 events per 8580 patient-years exposure, or 0.2 events per 100 patient-years.

Effect of dose modification on laboratory abnormalities

The strategy for modification of the study treatment regimen differed between the controlled core studies and the open-label extension studies. In the controlled double-blind period of the core studies, dose modification was limited to skipping an infusion of TCZ/placebo or

[4] Arthritis, Rheumatism and Aging Medical Information Systems (ARAMIS) database, National Data Bank for Rheumatic Diseases database
[5] RA patients in Nurses' Health Study and in UK General Practice Research database

interrupting the ongoing infusion of TCZ/placebo. In the extension studies, investigators, at their own discretion, were also allowed to skip the dose of TCZ or to decrease the dose from 8 mg/kg to 4 mg/kg. In all studies, investigators could also modify the dose of any concomitantly administered DMARD or other medications.

In the All Control population, reflective of the controlled periods of the Roche RA pivotal trials, 183 of 1555 patients in the control group (12%), 135 of 774 patients (17%) in the TCZ 4 mg/kg group, and 316 of 1870 patients (17%) in the TCZ 8 mg/kg group had at least one AE that led to dose modification. The rate of AEs that led to dose modifications was approximately 28 per 100 patient-years in the control group, 33 per 100 patient-years in the TCZ 4 mg/kg group and 34 per 100 patient-years in the TCZ 8 mg/kg group. The most common AEs leading to dose modification were infections and infestations, which were reported at a lower rate in the control group (~12 per 100 patient-years) than in the TCZ 4 mg/kg and 8 mg/kg groups (16 and 15 instances per 100 patient-years, respectively). AEs in the system-organ-class (SOC) of "Investigations" were also common, reported at a rate of 4.6 per 100 patient-years in the control and TCZ 4 mg/kg groups and 6.2 per 100 patient-years in the TCZ 8 mg/kg group, and primarily included abnormalities in liver function tests.

In the All Exposure population, 1821 of 4009 patients (45%) had at least one AE that led to dose modification. The overall rate of AEs that led to dose modifications was approximately 37 per 100 patient-years, which remained consistent over time. The types of AEs leading to dose modifications were consistent with the clinical experience reported to date. Infections and infestations were the most frequently reported events leading to dose modifications (~18 per 100 patient-years of exposure), and the most common infections were upper respiratory tract infection, bronchitis, nasopharyngitis, and sinusitis. The rates of infections that led to dose modifications remained relatively stable over time as well.

Abnormal liver function tests (transaminases and bilirubin) were the second most common AEs that led to a dose modification (approximately 3 instances per 100 patient-years). The overall rate of dose modifications due to neutrophil decreases was 1.4 instances per 100 patient-years.

Assessment of Dose Modification Strategy

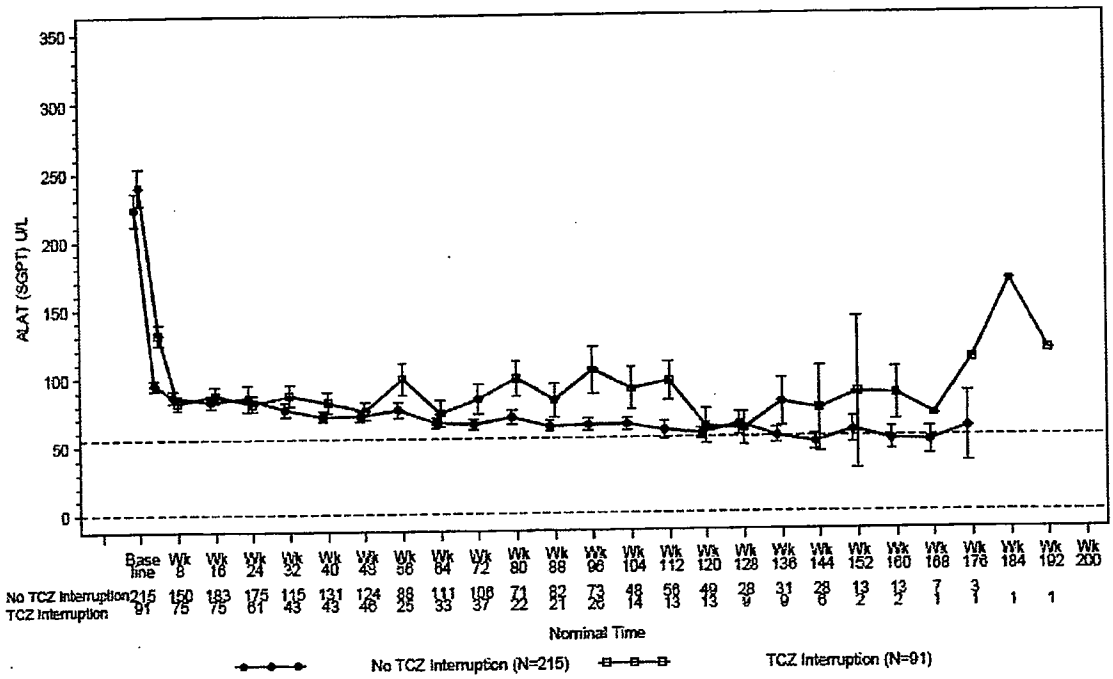
Overall, the results indicate that skipping or reducing the dose of TCZ to manage an AE was adequate to maintain patients on treatment. Of the 2050 AEs that led to either a skipped or reduced dose of TCZ, 1859 (91%) were successfully managed, in that they did not lead to withdrawal from treatment. More AEs were managed by skipping a dose of TCZ rather than reducing the dose from 8 mg/kg to 4 mg/kg. Of the 2050 AEs that led to either a skipped or reduced dose of TCZ, 1793 (87%) were managed by skipping a dose of TCZ.

The most common types of AEs leading to a skipped dose of TCZ were infections and infestations. The most common types of AEs leading to a reduction in the dose of TCZ from 8 mg/kg to 4 mg/kg were those in the "investigations" SOC, driven primarily by abnormalities in liver function tests. Of the 257 events managed with a dose reduction, 247 (96%) were sufficient to enable safe continuance of TCZ therapy.

Figure 2 below illustrates comparative ALT levels for patients who experienced elevation > 3 x ULN, and were managed by dose interruption (open squares in the figure) or no dose interruption (solid circles). Interestingly, ALT levels appear to decrease back toward normal levels regardless of whether TCZ doses were held or not.

Figure 2 Mean Plot Over Time for Patients Following First ALT Elevation >3x ULN (All Exposure Population)

SGtb_mn_at3_M Mean Plot of ALT (+/SE) Over Time for Patients following first ALT Elevation >3 ULN - All Exposure Population (Safety Popu



Source: Figure 12 of Complete Response Safety update

- **Immunogenicity**

Although tocilizumab is a recombinant human monoclonal antibody, a small proportion (approximately 4%) of patients developed anti-product antibodies. While development of these antibodies did not appear to affect overall safety (similar proportions of antibody positive and negative patients experience adverse events and serious adverse events), patients who developed these antibodies may have been more likely to experience anaphylaxis or an infusion reaction, although the proportion is still low (see Table 19 below).

The majority of patients who withdrew due to loss of efficacy (134/152, 88%) were anti-TCZ antibody negative, but these patients were a small fraction of the total number of TCZ-treated patients, most of whom did not experience loss of efficacy. However, a disproportionate number of patients developing positive neutralizing antibodies (66/127, 52%) withdrew for loss of efficacy, suggesting that these antibodies may in fact be interfering with treatment effects. This conclusion is further supported by an additional analysis of the 35/152 patients

withdrawing due to loss of efficacy who had previously achieved ACR50 or DAS-EULAR-"Good" responses. In this subset of patients, 14 (41%) had positive neutralizing antibodies.

Table 19 Immunogenicity and Possible Effects on Safety and Efficacy

Summary of Immunogenicity and Possible Effects on Safety and Efficacy			
Safety			
Proportion of All Exposure Pop	**Anti-TCZ positive patients 173/4009 (4%)**	**Anti-TCZ negative patients 3764/4009 (94%)**	**Missing n = 72**
Pts with ≥ 1 AE	159/173 (92%)	3482/3764 (92%)	-
Pts with > 1 SAE	39/173 (23%)	871/3764 (23%)	-
Anaphylaxis	5/173 (3%)	4/3764 (<1%)	-
Urticaria	1/173 (<1%)	58/3764 (2%)	-
Infusion Reaction	5/173 (3%)	12/3764 (<1%)	-
Withdrawal for loss of efficacy, n = 152	**Anti-TCZ Positive**	**Anti-TCZ Negative**	**Missing**
Screening Assay	15/152 (10%)	134/152 (88%)	3
Confirmation Assay	7/152 (5%)	142/152 (93%)	3
Neutralizing Assay*	66/152 (43%)	83/152 (55%)	3

* Total with positive neutralizing antibody assay, n = 127
Source: CR Update Tables STae_rr_spos, STae_rr_pos, Table 29

Effect of missed doses on immunogenicity

Of the 3937 patients who were tested for anti-TCZ antibodies, a total of 912 (23.2%) patients had at least one instance where there were ≥70 days between doses and they missed ≥2 consecutive infusions. Five hundred and twenty nine (58%) of these 912 patients had anti-TCZ assays performed both before and after missing consecutive doses and could therefore be evaluated for whether missed doses caused anti-TCZ seroconversion. Approximately 86% of evaluable patients were negative for anti-TCZ antibodies before and after missing ≥2 consecutive doses. Six patients (1.1% of the evaluable patients) who were negative for specific anti-TCZ antibodies prior to their missed infusions became positive for specific anti-TCZ antibodies after resuming infusions. Seven (1.3%) patients who were negative for neutralizing antibodies converted to anti-TCZ neutralizing antibody positive. The proportion of patients who became anti-TCZ positive following missed doses is lower than the overall proportion of patients who became anti-TCZ positive (173/3937 tested patients positive, 4%; 127/3937, 3%, of tested patients positive for neutralizing antibodies), suggesting that missing doses did not increase the likelihood of seroconversion.

- **Special safety concerns**

Gastrointestinal Perforations

A total of 25 gastrointestinal perforation events have been observed in the global RA program for TCZ, up from 16 events reported in the original BLA submission. The exposure-adjusted incidence of lower GI events in the TCZ program has increased from 0.15 to 0.21 events per 100 patient-years and the exposure-adjusted incidence of upper GI events remained the same. Both of these estimates are above rates found in RA patients in the United Health Care (UHC) and Marketscan databases (see Table 20 below), though the 95% confidence intervals are

overlapping, as per the applicant. The incidence is well below that observed with corticosteroids (0.39 per 100 patient-years), but appears to be higher than estimated incidence for TNF inhibitors (0.13 per 100 patient-years) [Table 21 in the complete response safety update, data not shown].

Table 20 Exposure Adjusted Incidence of Gastrointestinal Perforations in RA Patients

Exposure-Adjusted Incidence of GI Perforations in RA Patients						
	TCZ program Events	TCZ program Events/100 pt-yrs	UHC database Events/100 pt-yrs	Marketscan database Events/100 pt-yrs	Japanese Post-Marketing Data	
					Events	Events/100 pt-yrs
Upper GI	5	0.05	0.03	0.02	2	0.15
Lower GI	20	0.21	0.16	0.14	4	0.15
Total	25	0.27	0.18	0.16	6	0.22

Data cut-off February 6, 2009; 03-25-09 for Japanese post-marketing data
Sources: Tables 14 and 15 of 120 day safety update; section 4.1.13 from Roche 4-9-09, Table 19 of CR safety update

Demyelinating Disorders

Four additional cases of potential demyelinating neurologic disorders have been reported since the original BLA submission: a 36 year old female with a transient episode of cranial neuropathy, a 75 year old female who likely had symptoms due to chronic small vessel ischemia, a 50 year old male who may have had a central nerve etiology for left leg pain and hypoesthesia, and a 41 year old female who was diagnosed with multiple sclerosis (MS), but reported similar symptoms before starting TCZ treatment (see Table 21 below). Of all 8 cases reported thus far, only 3 cases appear to represent true demyelination, with 1 patient (with MS) reporting symptoms before TCZ treatment. Estimates of background incidence rates of demyelinating disorders in RA patients have not been reported. Thus it is not possible to determine relative risk of TCZ treatment with respect to demyelinating disorders, and there are too few events to draw definitive conclusions. Nonetheless, uncommon cases of demyelinating disorders have also been reported with other biologic immunosuppressives, and these have been placed in the Warnings section of approved labeling for these agents. It would be reasonable to similarly include mention of these adverse events in the Warnings section of the tocilizumab label.

Table 21 Demyelinating Adverse Events

Demyelinating AEs in the Tocilizumab Global Program								
Study	Event	Age/ Gender	TCZ dose	Doses prior to event	Latency (months)	Concomitant diagnoses	Outcome	Comments
WA18062/18696	L sided pos Babinski & tremor; MRI c/w white matter lesions & parietal lobe atrophy	64/M	8 mg/kg	11 to 14 (escape at week 16)	14	migraines hypothyroid peripheral vascular dz	tremor dx'd as benign essential tx with topiramate	withdrawn
WA17823	Blurred vision, dx with cataracts and bilateral optic neuritis	73/F	Blinded	8	8	on INH for pos PPD HTN, osteoporosis	No other demyel. lesions on MRI	continued
WA18062/18696	Progressive weakness & wt loss, dx as chronic idiopathic polyradiculoneuropathy	68/F	8 mg/kg	~11	~10	COPD, HTN, HLD DVT, osteoporosis	death	
MRA213JP/ MRA215JP	deteriorating mental status, dx as leukoencephalopathy	72/F	8 mg/kg	50	~50	Type II DM, HTN HLD, aortic stenosis osteoporosis	extensive white matter lesions neg w/u (inc. PML)	withdrawn
	Cranial neuropathy	36/F	8 mg/kg		~19	migraines, DM	resolved	continued
WA17824/18696	Occipital HA & scotoma; MRI w/ white matter lesions	75/F	8 mg/kg		~18	hx of right frontal meningioma	Dx c/w chronic small vessel ischemia	continued
WA18062/18696	leg pain & hypoesthesia	50/M	8 mg/kg		~26	hx of spinal fusion	EP: "central nerve disturbance"	continued
ML21469	polyneuropathy & nystagmus	41/F	8 mg/kg		3	hx of same sx before TCZ	Dx: MS	withdrawn

Source: BLA 125276 amendment 11 case narratives, complete response safety update

Pregnancy

A total of 31 pregnancies have occurred in 30 patients exposed to TCZ. Of these pregnancies, 5 are ongoing, 12 underwent therapeutic terminations, 7 spontaneous miscarriages occurred, 4 normal newborns were born, 1 infant died at 3 days of age from respiratory distress, 1 outcome was unknown and 1 was a false pregnancy (gestational trophoblastic tumor). Pregnancy events have been uncommon, consistent with study protocols that mandate use of contraceptive methods for study participants. This small cohort of patients, whose exposure was also confounded by potentially deleterious agents such as methotrexate, is not sufficient to draw definitive conclusions about the possible effect of TCZ on human reproduction and pregnancy. The applicant has agreed to establish a pregnancy registry to follow TCZ-treated patients who become pregnant and accrue additional data in this regard.

- **Safety Conclusions**

Overall, the safety data from the Roche pivotal trials and long-term extensions, and the global experience with TCZ, depict the profile of an immunosuppressant, with its inherent risks, such as serious infections. TCZ manifested effects on laboratory parameters, such as decreased white blood cell count, increases in lipids, and most significantly, liver enzyme elevation, although these continue to lack significant association with clinical adverse events. Malignancies have not increased over time, and are consistent with background rates of malignancy in RA patients. GI perforation events continue to slowly accrue, and in the

expanded experience submitted in this complete response safety update, the exposure-adjusted incidence of GI perforations appears to be elevated compared to other biologic immunosuppressive agents such as TNF inhibitors, but remains well below expected incidence associated with corticosteroid treatment. Demyelinating adverse events remain a rare occurrence, and the relative risk and role of TCZ treatment in the development of these adverse events is not well defined. These types of potential risks are not unique in the RA therapeutic armamentarium and have historically been handled via appropriate labeling and Risk Evaluation and Mitigation Strategies (REMS), consisting primarily of a Medication Guide and Communication Plan. I believe these measures should also be adequate in this case.

• Labeling

The proprietary name, "Actemra," has been reviewed by the Division of Drug Marketing, Advertising and Communication (DDMAC) and the Division of Medication Error Prevention and Analysis (DMEPA) and has been determined to be acceptable.

The proposed package insert will also require minor revisions. The most significant issue of note is the proposed indication of "moderately to severely active patients with rheumatoid arthritis." Although the applicant has performed a study in early RA patients (Study WA17824), the significant risks associated with tocilizumab treatment support its use as second-line treatment, after standard non-biologic DMARDs have been tried and found to be inadequate. Thus the indication will need to be revised to "moderately to severely active RA patients who have had inadequate response to one or more DMARDs."

• Recommendations/Risk Benefit Assessment

• Recommended Regulatory Action

I recommend approval, pending agreement can be reached on revisions to labeling and REMS.

• Risk Benefit Assessment

In the September 17, 2008 Complete Response letter, because of the evident dose-response relationship for both efficacy and safety variables, the Division advised the applicant to submit a reassessment of the benefit-risk balance of recommending only the 8 mg/kg dose, or consideration of a recommendation to start with a 4 mg/kg dose and increasing to the higher dose as needed and as tolerated.

In this submission, the applicant has re-evaluated the data and proposes the following revised dosing recommendations:

1) In patients who have had an inadequate response to one or more DMARDs, a starting dose of 4 mg/kg in combination with DMARDs may be considered, followed by an increase to 8 mg/kg based on clinical response.

2) In patients who have had an inadequate response to one or more TNF antagonists, a dose of 8 mg/kg is recommended.
3) If monotherapy is being considered, 8 mg/kg is recommended.

Table 22, below, describes an estimate of the potential benefit vs. potential risks of TCZ treatment in RA. This table has been updated from the table found in the clinical review of the original submission to include calculations based on the 4 mg/kg dose regimen, which is also being considered for approval in this complete response submission. Number-needed-to-treat/-harm (NNT/NNH) calculations were based on the 4 placebo-controlled studies, utilizing the comparison of TCZ 8 mg/kg + DMARD vs. placebo + DMARD from the 6-month controlled period. Only 3 of these placebo-controlled studies contained a comparison of TCZ 4 mg/kg + DMARD vs. placebo vs. DMARD and were used for the 4 mg/kg calculations. Based on average proportion of responders in these studies, as few as 3 patients would need to be treated to have at least one patient experiencing a benefit on the level of an ACR20 response, and as few as 7 patients would need to be treated to have at least one patient experiencing a benefit of the magnitude of an ACR70 response for the 8 mg/kg dose regimen. For the 4 mg/kg regimen, slightly more patients would require treatment for each patient experiencing ACR20, ACR50 or ACR70 responses.

During this period, the frequency of malignancy diagnoses and lipid-lowering agent starts was the same in the TCZ 8 mg/kg + DMARD group as for the placebo + DMARD group, resulting in a NNH of ∞. As a caveat, it should be noted that the proportion of patients experiencing malignancy, SAE, SIE, or needing to start lipid lowering agents all increased over the duration of the long-term extension studies. However, exposure-adjusted incidence of malignancies remained similar to the controlled period, and exposure-adjusted incidence of serious infections was lower. The rate of GI perforations may be elevated over background rates in RA but were an uncommon occurrence in the 6-month controlled period of the trials. For the 4 mg/kg treatment groups in these studies, the NNH for the various risks evaluated was not always greater than for the 8 mg/kg treatment groups. Compared to the 8 mg/kg treatment group, more patients required treatment with 4 mg/kg TCZ for each patient experiencing a serious infection or liver enzyme abnormality. No patients treated with 4 mg/kg experienced a GI perforation, resulting in a NNH of ∞. However, the exposure-adjusted incidence of malignancy was slightly higher in the 4 mg/kg group compared to the 8 mg/kg group, and lipid lowering agent starts were 1.5 x more frequent in the 4 mg/kg group than in the 8 mg/kg group. For these two risks, when the clinical data are evaluated in more detail, it appears that the impact of 4 mg/kg treatment and 8 mg/kg treatment are similar. Specifically, the number of malignancies is small in the 4 mg/kg group and the overall exposure experience is much less than for 8 mg/kg, and the effect of both doses on lipid parameter changes is equivalent.

Table 22 Risk Benefit Summary

Risk-Benefit Overview				
Clinical Activity	**Proportion Responding**		**Number Needed to Treat**	
	4 mg/kg	**8 mg/kg**	**4 mg/kg**	**8 mg/kg**
ACR20	46%	58%	~4	~3
ACR50	25%	36%	~6	~4
ACR70	10%	18%	~12	~7
Risks	**Frequency**		**Number Needed to Harm**	
	4 mg/kg	**8 mg/kg**	**4 mg/kg**	**8 mg/kg**
Serious Infection	4.7 per 100 pt-yrs	5.7 per 100 pt-yrs	~125	~56
Malignancy	1.6 per 100 pt-yrs	1.5 per 100 pt-yrs	1000	∞
GI Perforations	-	0.2 per 100 pt-yrs	∞	~385
Demyelinating AE	-	.05 per 100 pt-yrs	n.d.[a]	n.d.[a]
Liver enzyme abnormalities[b]	11 per 100 pt-yrs	18 per 100 pt-yrs	~14	~7
Lipid lowering agent starts	4.7 per 100 pt-yrs	2.8 per 100 pt-yrs	~56	∞

Data presented pertains to TCZ 8 mg/kg + DMARD group

NNT/NNH calculations based on comparison with placebo + DMARD, controlled period, exposure adjusted

a) not determinable-one event occurred during a placebo-controlled period, but tx remains blinded

b) based on most common "marked abnormality" of elevated ALT; no clinical hepatotoxicity events noted

Overall, the risk:benefit profile of TCZ in RA appears to be favorable, with many more patients potentially benefiting from treatment compared to those at potential risk. The aforementioned new dosing recommendations proposed by the applicant appear to be reasonable given the differences in the risk:benefit profile of the 4 mg/kg and 8 mg/kg dose regimens discussed above. Consistent with my conclusions from review of the data in the original BLA, I believe the clinical data support approval of BLA 125276. Nonetheless, many of the potential risks are significant, and will need to be accounted for in the package insert and REMS, which is discussed in further detail below.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)**

On November 14, 2008, Hoffman LaRoche was given additional specific guidance by the Agency regarding the contents of the REMS for tocilizumab. In this letter, the Agency notified the company that the REMS should contain a Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU), with attention to the risks of serious infections, gastrointestinal perforations, changes in liver function, decreases in neutrophil counts, decreases in platelet counts, elevations in lipid parameters, and demyelinating disorders and malignancies. The ETASU portion of the REMS was to be a restricted distribution program that would ensure that healthcare professionals prescribing and administering tocilizumab would be certified as having received training on and would attest to follow approved product dosing and administration instructions, including laboratory monitoring regimens and dose modification/interruption protocols, and adverse event reporting.

The REMS the applicant submitted with this Complete Response followed the Agency's instructions as per the November 14, 2008 letter to Hoffman LaRoche. However, in the intervening time period since that letter was issued, the Agency has had additional extensive internal discussions and determined that the adverse events and laboratory abnormalities associated with tocilizumab treatment are similar to those observed with other products approved to treat Rheumatoid Arthritis and do not warrant ETASU to ensure that the benefits of tocilizumab outweigh the risks. Therefore the company was notified by teleconference on November 3, 2009, and by letter on November 16, 2009, that a modified REMS proposal should be submitted to the BLA and that the revised REMS need not contain the ETASU.

This revised REMS, containing a Medication Guide, Communication Plan, and Timetable for Assessment of the REMS, was submitted to the BLA on November 25, 2009. The revised REMS is still undergoing review by the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK). My preliminary assessment of the revised REMS is as follows:

1) The Medication Guide is generally acceptable, but will require revisions.
2) The Communication Plan is proposed to target Rheumatologists and other healthcare professionals likely to prescribe tocilizumab, as well as healthcare professionals of other specialties that could be consulted or otherwise involved—infectious disease specialists, gastroenterologists/hepatologists, primary care providers, neurologists, and oncologists. Proposed communication vehicles include:
    a. a Dear Healthcare Provider letter,
    b. a Dear Pharmacist letter,
    c. Panel/poster/other printed materials to be distributed via the company-sponsored booth at professional society meetings,
    d. Printed information pieces in major professional journals to be sponsored quarterly for 3 years, or biannually for 3 years, as applicable

    The Communication Plan is acceptable, although the printed materials to be distributed will likely require some revisions.
3) REMS assessments are to be submitted to FDA 18 months, 3 years and 7 years post-approval. Details of these assessments are still under review, but the timing is acceptable.

- **Recommendation for other Postmarketing Requirements and Commitments**

1) Long-term observational safety studies

The intent of long-term safety studies is to identify delayed adverse events that may not readily manifest in the shorter duration of controlled clinical trials. The applicant has two ongoing long-term extension studies (WA18695/WA18696) that will allow for observation of patients with up to 5-years treatment. Patients completing the core studies were eligible to continue treatment in these extensions; as of the data cut-off for this submission, over 2500 patients have enrolled. Based on past experience with other biologics, these studies should be of sufficient size and duration to characterize most of the key adverse events of interest.

2) Cardiovascular outcomes study

Because TCZ treatment not uncommonly results in lipid parameter elevations, the Division advised the applicant in the first application cycle that a cardiovascular outcomes study would be necessary to better define the risk of treatment with respect to cardiovascular events. It was felt that no cardiovascular signal could be ruled in or out with the few events observed in the clinical trials and long-term extensions to date. The applicant was advised to design a study with "a sample size and duration sufficient to ensure that there are enough events to rule out a moderate increase in risk with TCZ."

In this submission, Roche provided their assessment of the feasibility of a cardiovascular outcomes study. They propose that an upper limit of 1.33 for the 95% CI of the hazard ratio would be too difficult to target due to the limited number of appropriate patients in the RA patient population. Thus, Roche proposes that a non-inferiority margin of 1.5 represents a reasonable upper limit for a 95% CI translating to "moderate" risk for increasing CV events in comparison with an anti-TNF biologic. To achieve a non-inferiority margin of 1.5 to detect differences in event rates between two agents, the point estimate would need to be 1.17 or less. Assuming there is no difference in the event rates between the treatment arms, it would be necessary to accrue approximately 256 CV events (fatal and non-fatal MI and stroke), which were both Clinical Event Committee adjudicated and fulfilling the modified intent-to-treat population criteria.

In order to reach this number of events in a reasonable time period, Roche proposes to enroll a "high risk" patient population, assuming an event rate of 2 per 100 patient-years, such a trial would require approximately 4,600 "high-risk" patients to be enrolled, which would require enrollment of over 50% of the available high risk RA population into the study if enrollment is to occur over a 2 year period. Even if extended to include a population from Europe, the available population is only increased by 7,500. Based on Roche's prior experience in conducting clinical studies, Roche believes even enrolling a global trial population with this number is not achievable in a two year period.

Roche further argues that the feasibility of a cardiovascular outcomes study is also challenged by confounders such as previous biologic treatment, need for switching to tocilizumab treatment as escape therapy, need for instituting lipid lowering agents for abnormal lipid parameters, unclear CV risk of the biological comparators (i.e. TNF inhibitors, which also appear to cause LDL and HDL elevation).

Further discussions will be needed internally, and with the applicant, to clarify details of the design and conduct of a cardiovascular outcome study with tocilizumab. These details need not be finalized prior to approval, though a timeline for this postmarketing study requirement will be. These timelines have not yet been negotiated at the time of this review.

3) Immunization studies

For products intended to suppress the immune response, such as tocilizumab, it is beneficial to know how the treatment might impact the response to immunization, in order to better inform clinicians how to handle desired immunizations for their patients; e.g., whether patients should

be brought up to date on immunizations before starting treatment, and whether treatment must be interrupted to achieve adequate responses to future immunizations. The applicant currently has such a study planned as a substudy of the long-term extension studies currently in progress. No additional details of this planned study have been submitted in this Complete Response.

4) Studies to achieve compliance with PREA

Polyarticular juvenile idiopathic arthritis (PJIA) is considered to be the pediatric equivalent of adult RA. Therefore, in accordance with the Pediatric Research Equity Act (PREA) of 2003, studies in PJIA are mandated. With the original BLA submission, the applicant has requested a deferral for patients age 2-17 with PJIA, and a waiver for children 0-2, since PJIA is extremely rare in this age group. These requests have been granted for other therapeutic biologics, as, for ethical reasons, it is desirable to have an adequate experience with the safety profile of a treatment in adults before proceeding with extensive studies in children. The applicant has already discussed details of their proposed Phase 3 program in PJIA and systemic juvenile idiopathic arthritis (SJIA) with the Agency. [b(4)

] The proposed study appears adequate to meet the requirements of PREA.

Summary Basis for Regulatory Action

Date	September 15, 2008
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # **Supp #**	125276
Applicant Name	Hoffmann-LaRoche
Proprietary / Established (USAN) Names	Actemra Tocilizumab
Dosage Forms / Strength	Intravenous 8 mg/kg every 4 weeks
Proposed Indication(s)	For the treatment of adult patients with moderate to severe active rheumatoid arthritis alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs
Action:	*Complete Response*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding tocilizumab (TCZ) and I refer the reader to the reviews in the action package for a more detailed discussion. Tocilizumab is a recombinant human monoclonal antibody that selectively binds to soluble and membrane-bound human interleukin 6 receptor (IL-6R). The action of tocilizumab inhibits the binding of IL-6 to the receptor and therefore blocks the subsequent signaling cascade of IL-6. IL-6 is a cytokine that is a mediator of inflammation and is involved in the production of acute phase reactants, including C-reactive protein (CRP).

Tocilizumab has proven efficacy when given every four weeks intravenously for both an 8 mg/kg, and a 4 mg/kg dose in subjects who have had inadequate clinical response to methotrexate (MTX) or anti-TNF agents. The 8 mg/kg dose demonstrated, in what appeared to be a fair comparison, that it was not inferior, and perhaps was superior, to MTX in MTX naïve subjects. When using American College of Rheumatology (ACR) 20, 50 and 70 response as a method to determine efficacy, it appears that the 8 mg/kg dose may have, on average, somewhat greater efficacy than the 4 mg/kg dose for most of the ACR parameters, but not by a great margin. Therefore, tocilizumab has demonstrated efficacy, but as will be discussed below, there are concerns regarding the appropriate dose and whether, due to safety concerns, the indication should be narrowed to patients who have not responded to a DMARD or TNF inhibitor until further safety information is available.

Tocilizumab demonstrated the following safety concerns:

1) Increased incidence of serious infections that was dose related compared to placebo
2) Increased incidence of laboratory abnormalities compared to placebo including
    a) Decreased white blood cell count (WBC)

b) Decreased platelets

c) Increases in lipid parameters (appears dose related). The potential of this to translate into cardiovascular events is unknown

d) Liver enzyme elevations

3) Gastrointestinal (GI) perforations that may be dose related

4) Demyelinating events, both central and peripheral

While there were decreases in WBC and platelet counts compared to placebo, the mean values still remained within normal limits. As noted above, the incidence of serious infections and GI perforations, as well as some of the other laboratory abnormalities, appear to be dose-related, which should give cause for careful consideration regarding the appropriate dose for therapy initiation. Regarding the liver enzyme elevations, there was one concerning case and some controversy as to whether this case fulfilled criteria for Hy's Law that I will discuss further below. Also for further discussion below, is what potential impact the increase in lipid parameters may have regarding adverse cardiovascular effects in a RA population, which is already at higher risk for cardiovascular events compared to a non-RA population. The validity of these safety concerns is still somewhat uncertain and will warrant a Risk Evaluation and Mitigation Strategy (REMS) until more information becomes available.

The nonclinical pharmacology/toxicology section of this application is incomplete as the sponsor did not submit peri-natal and post-natal reproductive toxicology studies as have been required prior to approval of all biologic agents used to treat RA. This has been thoroughly discussed in Dr. Rappaport's review. I agree with his conclusions and will not discuss this further.

There are major deficiencies at the manufacturing facility in Japan, including infestations, failure of sterile processes and the use of in one testing procedure. The formal review is pending at this time, but we have been informed that the review team will recommend a CR action until the site can remediate the deficiencies. b(4)

The nonclinical and manufacturing concerns above preclude marketing at this time which will result in my recommending a complete response action.

Efficacy

This has been thoroughly covered in Drs. Okada and Siegel's reviews and I will focus on the 4 mg/kg vs 8 mg/kg issue. Efficacy for this application was evaluated by five studies, four being placebo-controlled (WA17822, WA 17823, WA 18062 and WA 18063) and a non-interiority trial (WA17824). The design of these trials is summarized in the table below from Dr. Okada's review (page 19).

Table 1: Key Design Features of the 5 Pivotal Phase 3 Studies and the 2 Open-Label Extensions

	WA17822	WA17823	WA17824	WA18062	WA18063	WA18695	WA18696
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	OL extension study; approximately 5 years*	OL extension study; approximately 5 years*
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	Patients completing treatment in WA17822	Patients completing treatment in WA17824, WA18062, WA18063, WP18663
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 <u>or</u> 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)	1 arm: Tocilizumab: 8 mg/kg iv every 4 weeks plus MTX	1 arm: Tocilizumab: 8 mg/kg iv every 4 weeks alone or plus MTX / other 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	537**	1902**
Primary Endpoint at Week 24	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	Long term safety/efficacy	Long term safety/efficacy

DB = double blind, R = randomized. PC = placebo controlled, DD = double dummy. OL = open label
* Or when tocilizumab becomes commercially available in the participating country, or when the sponsor decides to discontinue the study.
** Patients were not randomized into WA18695 and WA18696, but enrolled from studies WA17822, WA18063, WA18062 and WA17824

Applicant Table 1 of Module 2.7.3 Summary of Clinical Efficacy

The results of these studies are summarized in the table below from Dr. Okada's review (page 28).

Table 2 Proportion of ACR20/50/70 Responders at Week 24

Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment (ITT Populations)					
Study	Pbo + DMARD**	TCZ 4mg/kg + DMARD**	TCZ 8mg/kg + DMARD**	p-value (4 mg/kg)	p-value (8 mg/kg)
Patients with incomplete response to MTX or other DMARDs					
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
WA18063	(n=413)		(n=803)		
ACR20	24		61		<0.0001
ACR50	9		38		<0.0001
ACR70	3		20		<0.0001
Patients with incomplete response to prior TNF inhibitor treatment					
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

MTX naive/Early RA patients					
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 for primary analysis population

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 19 of WA17822 CSR, Tables 17 & 18 of WA17823 CSR, Tables 17 & 22 of WA17824 CSR Tables 21 & 23 of WA18062 CSR, and Tables 17 & 20 of WA18063 CSR

The results of these studies clearly demonstrate that the 4 mg/kg and 8 mg/kg dose of tocilizumab is effective in subjects with incomplete response to MTX or TNF inhibitor treatment. Drs. Okada and Siegel note in their reviews that the secondary endpoints are also consistent with these results. In those trials that contained both a 4 and 8 mg/kg dose arm, the 8 mg/kg arm demonstrated a numerically greater point estimate than the 4 mg/kg arm. It is important to remember however, that this reflects mean averages and does not predict that 8 mg/kg will necessarily be more effective than 4 mg/kg for any particular individual patient.

It is interesting to note that in study WA17824 that the 8 mg/kg dose not only proved non-inferior to MTX, but demonstrated impressive and robust superiority in what would seem to be a fair comparison.

An Advisory Committee (AC) meeting was convened on July 29, 2008 for this product. During that meeting, there was a discussion of whether the initial dose, when viewed in conjunction with potential dose related toxicities, should be 4 mg/kg or 8 mg/kg. Dr. David Felson, as noted in Dr. Siegel's review, pointed out that he felt most of the individual components of the ACR showed little difference with the exception of the CRP. As such, he felt consideration should be given to a starting dose of 4 mg/kg.

The table below obtained from Dr. Okada's review (page 33), demonstrated the mean change in the ACR components.

Table 3 Mean Change in ACR Components, Baseline to Week 24

Summary of Change in ACR Components, Baseline to Week 24, by Trial and Treatment													
RA Population:	DMARD Inadequate			DMARD Inadequate			Early RA		TNF Inadequate			DMARD Inadeq.	
		WA17822			WA17823			WA17824		WA18062			WA18063
	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	MTX n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 8 n (%)
ITT Population (PP for WA17824)	204	213	205	393	399	398	259	265	158	161	170	413	803
SJC (66 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 261	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-4.3	-8.5	-10.5	-2.5	-7.4	-8.5	-7.8	-11.7	-0.5	-6.8	-7.8	-4.9	-10.3
Adjusted Mean Diff.	-	-4.2	-6.2	-	-4.8	-5.9	-	-3.9	-	-6.2	-7.2	-	-5.5
95% CI of Difference	-	(-6.1,-2.3)	(-8.1,-4.2)	-	(-6.1,-3.5)	(-7.2,-4.6)	-	(-5.7,-2.0)	-	(-9.0,-3.5)	(-9.9,-4.5)	-	(-6.7,-4.3)
TJC (68 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 264	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-7.4	-14.5	-17.1	-4.9	-12.1	-14.0	-13.5	-17.1	0.3	-10.5	-14.8	-8.5	-15.7
Adjusted Mean Diff.	-	-7.0	-9.6	-	-7.2	-9.1	-	-3.6	-	-10.8	-15.1	-	-7.1
95% CI of Difference	-	(-10.0,-4.1)	(-12.6,-6.7)	-	(-9.2,-5.2)	(-11.1,-7.1)	-	(-6.3,-1.0)	-	(-14.6,-7.1)	(-18.8,-11.4)	-	(-8.9,-5.4)
Patient Global (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 316	n = 230	n = 242	n = 61	n = 106	n = 129	n = 322	n = 729
Adjusted Mean*	-17.8	-28.8	-32.7	-18.4	-24.9	-25.7	-29.5	-33.5	-15.4	-25.4	-32.8	-16.3	-33.2
Adjusted Mean Diff.	-	-10.9	-14.9	-	-6.5	-7.3	-	-4.1	-	-10.0	-17.4	-	-16.8
95% CI of Difference	-	(-17.1,-4.8)	(-20.9,-8.9)	-	(-11.4,-1.6)	(-12.1,-2.4)	-	(-9.3,+1.2)	-	(-20.3,+0.3)	(-27.6,-7.0)	-	(-20.5,-13.2)
Physician Global (mm)	n = 123	n = 158	n = 173	n = 214	n = 307	n = 320	n = 229	n = 242	n = 61	n = 106	n = 127	n = 322	n = 733
Adjusted Mean*	-32.7	-38.3	-41.6	-28.2	-34.0	-38.3	-31.5	-41.6	-20.0	-30.5	-38.2	-21.6	-35.9
Adjusted Mean Diff.	-	-5.6	-9.0	-	-5.8	-10.1	-	-10.1	-	-10.5	-18.2	-	-14.4
95% CI of Difference	-	(-10.5,-0.8)	(-13.8,-4.2)	-	(-9.6,-1.9)	(-14.0,-6.2)	-	(-14.2,-6.0)	-	(-18.6,-2.5)	(-26.3,-10.0)	-	(-17.3,-11.4)
Patient's Pain (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 317	n = 231	n = 242	n = 61	n = 105	n = 129	n = 322	n = 730
Adjusted Mean*	-14.0	-25.0	-29.8	-13.1	-19.3	-22.2	-29.5	-31.5	-8.6	-21.0	-32.5	-12.8	-29.9
Adjusted Mean Diff.	-	-11.0	-15.8	-	-6.2	-9.1	-	-2.0	-	-12.4	-23.9	-	-17.1
95% CI of Difference	-	(-17.0,-5.0)	(-21.7,-9.9)	-	(-10.9,-1.5)	(-13.9,-4.4)	-	(-7.1,+3.1)	-	(-22.1,-2.6)	(-33.7,-14.1)	-	(-20.8,-13.4)
CRP (mg/dL)	n = 122	n = 157	n = 172	n = 214	n = 308	n = 321	n = 230	n = 242	n = 63	n = 106	n = 129	n = 324	n = 727
Adjusted Mean*	-0.35	-1.66	-2.51	-0.14	-0.70	-1.89	-1.81	-2.85	-0.06	-1.40	-2.58	-0.27	-2.19
Adjusted Mean Diff.	-	-1.30	-2.16	-	-0.57	-1.76	-	-1.04	-	-1.34	-2.52	-	-1.93
95% CI of Difference	-	(-2.01,-0.59)	(-2.86,-1.46)	-	(-1.00,-0.13)	(-2.19,-1.32)	-	(-1.67,-0.41)	-	(-2.54,-0.15)	(-3.72,-1.32)	-	(-2.32,-1.54)
ESR (mm/hr)	n = 122	n = 157	n = 174	n = 211	n = 304	n = 318	n = 229	n = 240	n = 62	n = 107	n = 129	n = 325	n = 732
Adjusted Mean*	-7.1	-25.5	-39.5	-7.1	-19.4	-34.6	-15.1	-37.2	-3.0	-19.7	-37.2	-4.7	-35.6
Adjusted Mean Diff.	-	-18.3	-32.3	-	-12.3	-27.5	-	-22.1	-	-16.7	-34.2	-	-30.9
95% CI of Difference	-	(-24.3,-12.4)	(-38.2,-26.5)	-	(-16.7,-8.0)	(-31.9,-23.2)	-	(-27.2,-17.1)	-	(-25.4,-8.1)	(-43.0,-25.5)	-	(-34.2,-27.6)
HAQ-DI	n = 101	n = 126	n = 141	n = 197	n = 292	n = 301	n = 230	n = 243	n = 62	n = 106	n = 130	n = 322	n = 724
Adjusted Mean*	-0.34	-0.52	-0.55	-0.30	-0.41	-0.50	-0.48	-0.70	-0.05	-0.31	-0.39	-0.20	-0.47
Adjusted Mean Diff.	-	-0.18	-0.21	-	-0.10	-0.19	-	-0.22	-	-0.25	-0.34	-	-0.27
95% CI of Difference	-	(-0.34,-0.02)	(-0.37,-0.05)	-	(-0.20,-0.00)	(-0.30,-0.09)	-	(-0.22,-0.34)	-	(-0.42,-0.09)	(-0.51,-0.17)	-	(-0.34,-0.20)

*ANOVA

LOCF used for tender and swollen joint counts if missing or patient entered escape

No imputation used for missing HAQ score, CRP, ESR, and VAS assessments

Adapted from Tables 23 and 29 of WA17822 CSR, Tables 22 and 27 of WA17823 CSR, Tables 32 and 38 of WA17824 CSR, Tables 33 and 38 of WA18062 CSR, and Tables 25 and 30 of WA18063 CSR

While there is a distinct differential in the acute phase reactant components between the 4 and 8 mg dosages, there are also consistent differences in swollen joint count (SJC) and tender joint count (TJC) such that, on average, the 8 mg/kg dose accounts for 1 to 5 joint difference improvements depending on the trial and parameter (baseline pre-treatment for TJC and SJC was approximately 18 and 30 respectively). There are also dose related differences in the other parameters, small in magnitude, but consistent. As such, I think that there is a dose related clinical difference for the population on average between the 4 mg/kg and 8 mg/kg dose that may translate into benefit for an individual.

Below are responder analyses by Dr. Buenconsejo (obtained from Dr. Okada's review, page 36).

Percentage improvement in Disease Activity, ACRn, at Week 24

Analyses by Joan Buenconsejo, Ph.D.

X axis = Percentage improvement in disease activity, ACRn, scale 0-100
Y axis = Percent of patients improved, scale 0-100
WA17822, 17823, 18062: Blue line = TCZ 8 mg/kg, Black line = TCZ 4 mg/kg, Red line = Placebo
WA18063: Black line = TCZ 8 mg/kg, Red line = Placebo

Figure 1 Study WA17822

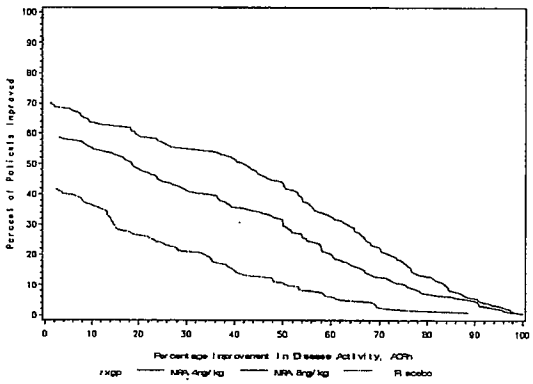


Figure 2 Study WA17823

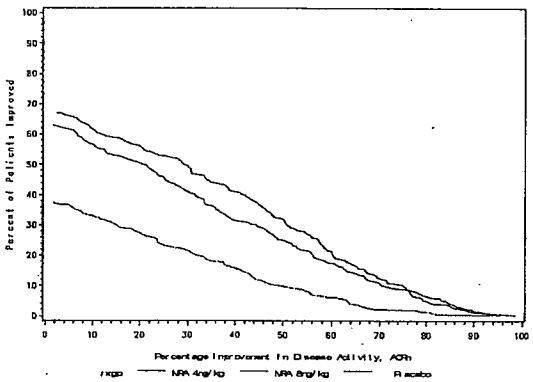


Figure 3 Study WA18062

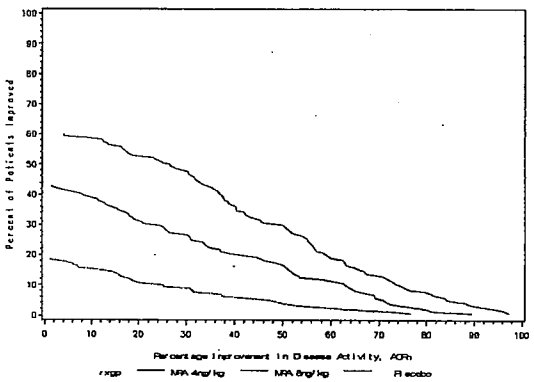
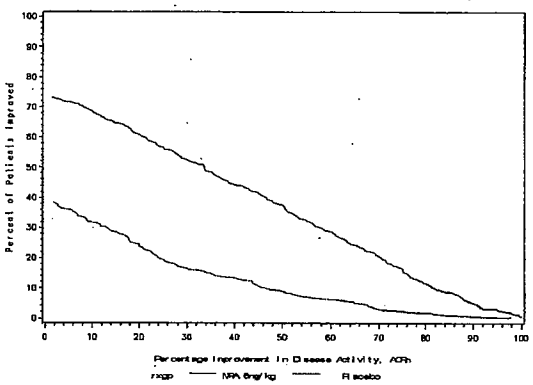
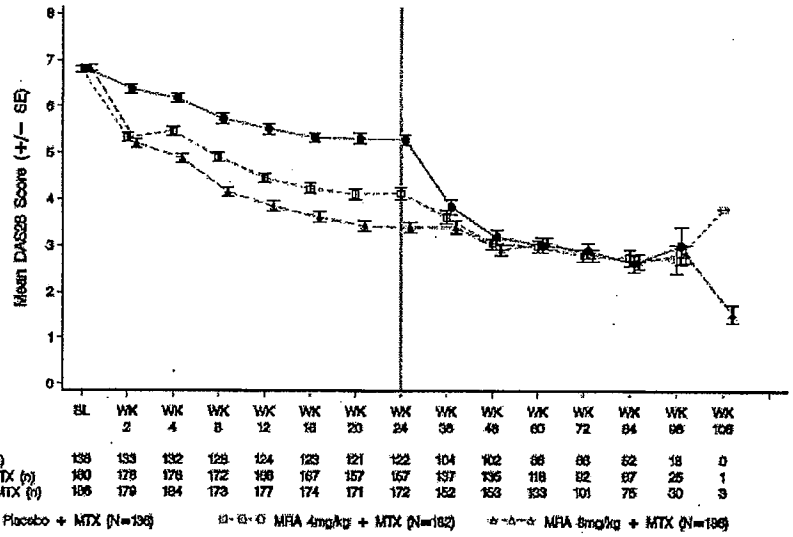


Figure 4 Study WA18063



These results demonstrate that for individual subjects, there are those receiving 4 mg/kg who can be expected to have resultant ACR responses equivalent to those in the 8 mg/kg group. What we cannot answer from this is whether, in a controlled comparison, subjects receiving 4 mg/kg would experience incremental improvement if they were then exposed to the 8 mg/kg dose. We can get some information from the long term extension, bearing in mind that this is open label data. The graph with this data is below and was provided to me by Dr. Siegel.

Figure 15 Mean DAS28 in the WA17822 Core Study ITT Population



LOCF used for tender and swollen joint counts. No imputation used for ESR and Patient's Global Assessment of Disease Activity VAS.
Escape patients are excluded.

Program :/opt/BIOSTAT/prod/bd11935m/m11935e/Eqp/DAS.sas / Output :/opt/BIOSTAT/prod/bd11935m/m11935e/reports/EQpDASearwa17822L.cgm
25SEP2007 12:48

Best Possible Copy

This does give some indication that individual subjects on 4 mg/kg may receive some incremental benefit when transferred to 8 mg/kg, keeping in mind that this is an open label extension, but as I will discuss with the safety concerns described below, I would advocate that the 4 mg/kg dose should be available to clinicians as an option for their individual patient and should be used with initial dosing.

Safety

Given that the targets of tocilizumab are mediators of inflammation and immunity, we would expect that this drug would have immunosuppressive properties and the adverse event profile common to immunosuppressive drugs such as infection, malignancy or autoimmunity.

Serious infections

Serious infections events (SIE) were more frequent with tocilizumab 8 mg/kg than with 4 mg/kg, both of which were higher than with placebo (5.7 vs. 4.7 vs. 3.9 SIE per 100 pt-yrs). There were also two cases of opportunistic infection that occurred in subjects receiving tocilizumab (pneumocystis jiroveci pneumonia-4 mg/kg arm and mycobacterium avium intracellulare pneumonia-8 mg/kg arm) compared to none in the non-tocilizumab.
The were not any reports of reactivation of latent tuberculosis infection during the trials despite a world-wide distribution of study sites and the lack of mandated tuberculosis screening or prophylaxis, although 52 patients had a history of TB or positive PPD prior to drug therapy. There were two cases of TB in the long-term extensions with one case of

urinary tract infection in a subject without TB risk factors or exposures and one septic arthritis in a subject who was PPD negative.

Based on these results, careful monitoring of patients for opportunistic infection, as with all immunosuppressive drugs, should occur.

Malignancy

Malignancy in tocilizumab treated subjects did not appear to be increased compared to controls, but there is limited data upon which to draw any final conclusions and the controlled data was only from six months of exposure.

Autoimmunity

Of the subjects tested, 1.8% tested positive for anti-TCZ antibodies in the six month safety population, not associated with loss of efficacy. Six patients experienced anaphylactic reactions, with three testing positive for anti-TCZ antibodies (1 was negative and two were not tested), all of which resulted in withdrawal. Dr. Okada stated that the frequency and severity of these events appear to be consistent with those observed with currently approved biologic treatments for RA.

Gastrointestinal perforations

IL-6 receptors are present on neutrophils and T-cells which may be found throughout the GI tract, and gp130 receptors, through which soluble IL-6/IL-6R may have effects, are present ubiquitously. Therefore there are a number of plausible effects of IL-6 blockade on the GI tract and it is difficult to predict what the net effects of blockade might be. There were three gastrointestinal (GI) perforations during the six-month controlled trial period. This included one upper (duodenal) and two lower, all occurring in subjects receiving tocilizumab 8 mg/kg. During the controlled trial period, approximately 2.5x more subjects were exposed to 8 mg/kg compared to 4 mg/kg (774 subjects randomized to tocilizumab 4 mg/kg + MTX vs. 1870 subjects randomized to tocilizumab 8 mg/kg + DMARD or monotherapy). There were 11 total GI perforations in the database which included long-term extension data. All the perforations were in subjects receiving 8mg/kg, but that was the only dose used in the long-term extensions. Dr. Okada notes that there were a total of 16 GI perforations in 15 patients (one patient with both and upper and lower GI perforation) in the global RA program which includes data from Roche and Chugai studies. She compares this to the data in the United Health Care database and Marketscan database below (page 66 of her review).

Table 4 Exposure Adjusted Incidence of GI Perforations

Exposure-Adjusted Incidence of GI Perforations in RA Patients				
	TCZ program Events	TCZ program Events/100 pt-yrs	UHC database Events/100 pt-yrs	Marketscan database Events/100 pt-yrs
Upper GI	4	0.05	0.03	0.02
Lower GI	12	0.15	0.16	0.14
Total	16	0.20	0.18	0.16

Data cut-off December 31, 2007

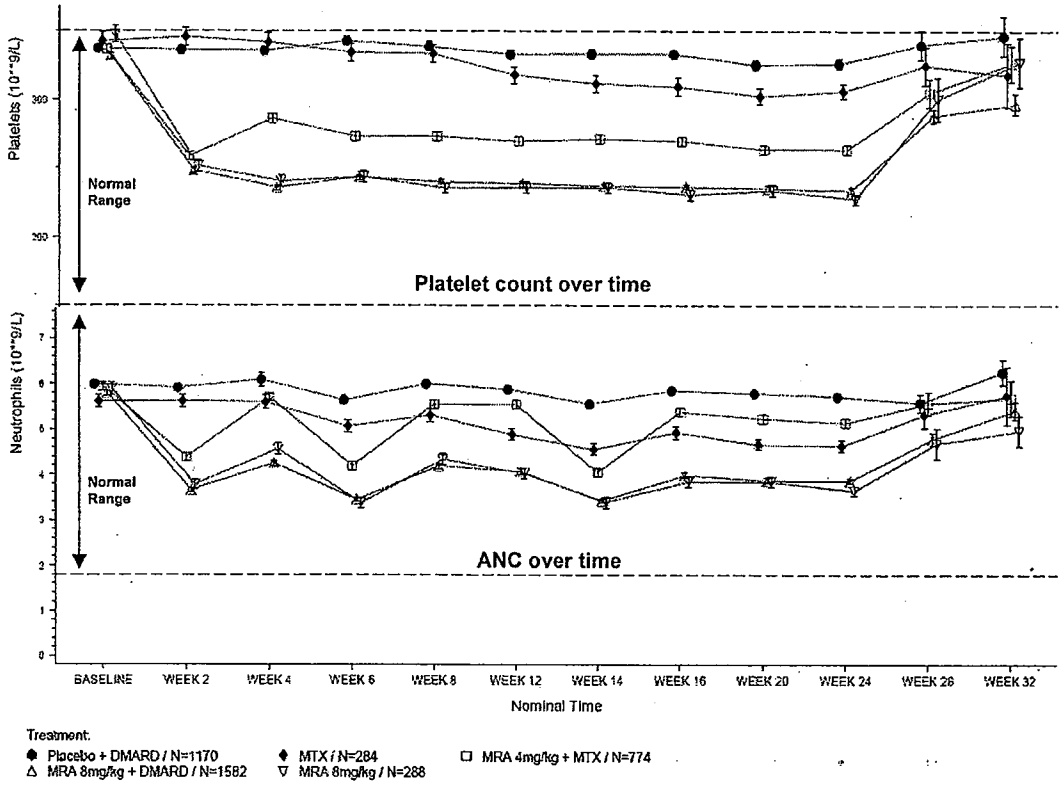
Sources: Tables 14 and 15 of 120 day safety update

This would seem to indicate that there is a higher rate of upper GI events and an equivalent rate of lower GI events if compared to a population database. However, I do not think that this totally explains away any concern with the 8mg/kg dose as no events occurred in the placebo (DMARDs and MTX=1454) or tocilizumab 4 mg/kg arms and these arms combined had more subjects than the tocilizumab 8 mg/kg arm during the 6 month randomization period. Even though there are few events, there seems to be an imbalance of events in the 8 mg/kg arm. As such, the data contained in this application would seem to require an advisement for cautious use in patients with a history of peptic ulcer disease or diverticulitis (?diverticulosis) and therapy with the lowest dose or perhaps avoidance of TCZ unless all other products have failed.

Platelet and WBC

Platelet and WBC counts were lower in the TCZ arms and this effect appeared dose related as seen in the graph below (page 72 of Dr. Okada's review).

Figure 15 Platelet Counts and ANC over time



Only worst values within a time window per patient are summarized. Escape data excluded.
Taken from Figures 2 and 3 of Module 2.7.4 Summary of Clinical Safety

Dr. Okada's review indicates that the decreased platelet count was not associated with bleeding events. Dr. Okada did not find cases of SIE in patients with Grade 3 or Grade 4 neutropenia. It is unclear if the dose related decrease in WBC with tocilizumab 8 mg/kg compared to 4 mg/kg would result in greater susceptibility to infections, although the SIE, like neutropenia, appeared dose related.

Liver enzyme elevations

Liver enzyme elevations were observed more frequently in TCZ + MTX treated subjects than in controls or TCZ only therapy. This is demonstrated in the table below (Dr. Okada's review, page 74).

Table 5 Hepatobiliary Worst Values

Hepatobiliary Worst Values in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
		6-months pooled safety population						Long term safety population
	range	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	2562
AST (U/L)								
normal	0-40	967 (83)	201 (71)	498 (64)	902 (57)	220 (76)	1620 (61)	1319 (51)
>ULN to 3 x ULN	41-120	194 (17)	74 (26)	264 (34)	646 (41)	64 (22)	974 (37)	1176 (46)
>3 x ULN to 5 x ULN	121-200	3 (0.3)	5 (2)	8 (1)	29 (2)	1 (0.3)	38 (1)	53 (2)
>5 x ULN to 8 x ULN	201-320	-	1 (0.4)	1 (0.1)	1 (0.1)	1 (0.3)	3 (0.1)	7 (0.3)
>8 x ULN	>320	1 (0.1)	-	-	2 (0.1)	1 (0.3)	3 (0.1)	2 (0.1)
ALT (U/L)								
normal	0-55	877 (75)	172 (61)	376 (49)	714 (45)	176 (61)	1266 (48)	991 (39)
>ULN to 3 x ULN	56-165	270 (23)	95 (33)	349 (45)	763 (48)	105 (36)	1217 (46)	1370 (53)
>3 x ULN to 5 x ULN	166-275	15 (1)	11 (4)	36 (5)	80 (5)	4 (1)	120 (5)	170 (7)
>5 x ULN to 8 x ULN	276-440	1 (0.1)	2 (0.7)	10 (1)	21 (1)	1 (0.3)	32 (1)	20 (0.8)
>8 x ULN	>440	2 (0.2)	1 (0.4)	-	2 (0.1)	1 (0.3)	3 (0.1)	7 (0.3)
Total Bilirubin (µmol/L)								
normal	0-17	1155 (99)	279 (98)	724 (94)	1438 (91)	264 (92)	2426 (92)	2250 (88)
>ULN to 3 x ULN	18-51	9 (0.8)	2 (0.7)	46 (6)	141 (9)	23 (8)	210 (8)	308 (12)
>3 x ULN to 5 x ULN	52-85	1 (0.1)	-	-	1 (0.1)	-	1 (0.03)	-
>5 x ULN to 8 x ULN	86-136	-	-	-	-	-	-	-
>8 x ULN	>136	-	-	1 (0.1)	-	-	1 (0.03)	-

*Includes MTX

Escape data are excluded

Sources: Tables stb_shift_btow_bchem of Module 2.7.4 Summary of Clinical Safety and 120 day safety update

The TCZ arms of 4 mg/kg + MTX and 8 mg/kg + DMARD had 5% elevations of ALT to 3x ULN to 5X ULN compared to 4% for the MTX arm and 1% for the placebo + DMARD arms, while the TCZ 8 mg/kg arm by itself, without the combination of a DMARD, had only 1% elevation. The data indicate that the combination of MTX with TCZ may carry a greater risk of transaminitis than when either drug is given alone. There was one case that had transaminase elevation (ALT) > 3x ULN with concomitant elevation of bilirubin > 2x ULN in a subject that was receiving the combination of MTX and TCZ 8 mg/kg. This case is well documented in Drs. Okada, Siegel and Rappaport's reviews and Dr. John Senior's consult and I would refer the reader to their reviews for all the details. I mention it here as there has been some controversy as to whether this represents a 'Hy's Law' case and I think it warrants some discussion.

Hy's Law criteria is used to define a population that has experienced drug induced liver injury (DILI) that may be at risk to not adapt to the injurious agent such that they may progress to liver failure. We currently conceptualize DILI as have six levels of severity as demonstrated in the table below from Dr. Senior's consult.

Levels of DILI Severity

5	Death
4	Acute Liver Failure
3	Serious: Sick, Hospitalized
2	Detectable Slight Functional Loss
1	Just Enzyme Elevations; Most People Adapt
0	Patients Tolerate Exposure - No Adverse Effects Seen

We have defined Hy's law criteria to require both elevated serum transaminase (ALT > 3x ULN) AND increases in total bilirubin concentration (>2x ULN) as a method to identify those subjects at level 2 which we feel indicates enough damage such that function is compromised and the subject is at risk to progress to liver failure. This is contrasted to those that only have serum transaminase elevation indicating DILI, but normal bilirubin such that liver function is not yet comprised. These subjects are considered to be at level 1 in the table above and are not felt to be at as high a risk for further progression to hepatic failure as those that are at level 2. One caveat to the evaluation is that to be considered a true Hy's law case, no other explanation can be found that might explain the combination of increased transaminase and total bilirubin other than the drug. Others reasons can include viral hepatic infections, cholestasis due to bile duct obstruction or Gilbert's Syndrome.

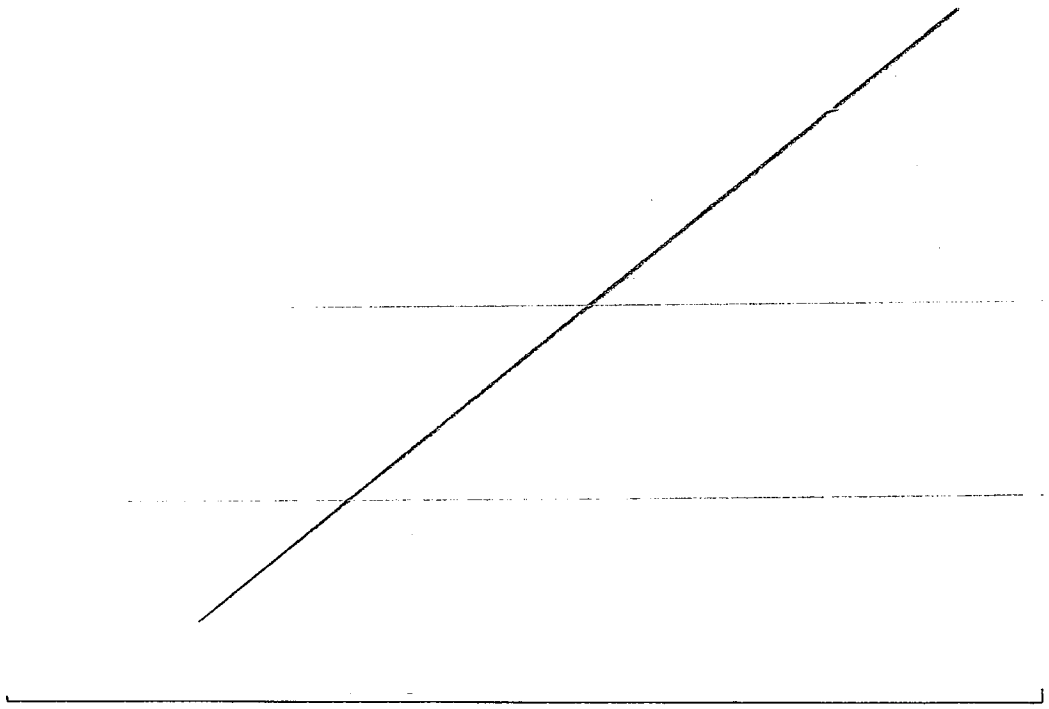
Using Hy's law criteria has proven very successful at identifying drugs that may carry risk for causing severe liver toxicity and estimating rates of liver failure that might be expected if the drug were to be marketed. However, as stated in our guidance, the implications of these findings may be different in patients with existing liver disease such as fatty liver disease, NASH, or chronic hepatitis C or B, with bilirubin metabolism abnormalities (Gilbert's syndrome), and in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir[1].

So it is important to remember that Hy's Law, in and of itself, is a definition and method of trying to identify subjects that may have level 2 DILI. Those subjects that may have other confounding issues such as viral hepatitis infections, fatty liver, NASH or Gilbert's may also have DILI, and may be at level 2 or above, but they may have elevations of bilirubin for

[1] Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. October 2007

reasons other than drug injury such that it confounds the use of bilirubin as a criteria. As such, subjects with underlying conditions probably cannot technically be called a 'Hy's Law' case even if they do have DILI and the Agency has not yet determined how to use the bilirubin laboratory abnormalities as a guide to determine if the DILI has advanced to Level 2.

It is important in this application as there is one subject that meets the criteria for Hy's law. This subject had received TCZ 8 mg/kg for many months without elevation of LFT's. She then was started on MTX 20 mg a day (without titration) and subsequently had increases in AST to 16x normal (or 31x-there is some confusion regarding the data sent from the sponsor) and total bilirubin greater than 2x ULN. Both drugs were stopped and the subject's LFT elevation resolved. She subsequently was re-challenged with both drugs and had elevations of her LFT's that resulted in stoppage of therapy. Her rechallenge occurred in such a way that it is not possible to determine if the offending agent was MTX, TCZ or the combination. This is demonstrated in the graph below from Dr. Senior's consult.



b(4)

The sponsor is contending that this patient had Gilbert's and therefore does not represent a Hy's Law case. Dr. Senior feels that this case clearly represents DILI and that, while he does have some reservations regarding the quality of the data that has been sent in, the subject probably does have Gilbert's. As such, this case cannot be technically labeled as a 'Hy's Law' case if in the end she does have Gilbert's Disease. However, I would contend that, semantics aside, what we are really interested in is whether this case represents level 2 liver damage. Dr. Senior does not feel that it does, as he feels that the bilirubin level is not high enough, but he cannot quantify for me what level of bilirubin rise he would expect. I would note, that the

level of ALT elevation in and of itself is concern (discussed below) and I am not convinced that this does not represent level 2 damage. As such, since we are faced with uncertainties, and we have seen that the combination of TCZ and MTX leads to increase percentages of LFT elevations and may be problematic, I feel that that we should err on the side of safety such that the burden is upon the sponsor to conclusively prove that this does not represent Level 2 damage, not upon us to prove that it doesn't. I would stress that it is quite likely that patients in clinical practice will frequently experience the combination of MTX and TCZ. In lieu of their not being able to demonstrate that this subject did not have level 2 DILI (and I don't see how they can), I feel the sponsor should generate more data and institute careful monitoring of LFTs until we have more experience with TCZ. I would also note that the marked elevation of ALT seen in this subject, while perhaps overly sensitive, in and of itself is concerning as stated in the guidance[1]:

> **Marked elevations of AT to 5x-, 10x-, or 20xULN in smaller numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group**
>
> Virtually all severely hepatotoxic drugs show such cases, indicating high sensitivity for predicting severe DILI, but, again, some drugs such as tacrine and others that are not severely hepatotoxic also can cause AT elevations to this degree, so that specificity of this finding is suboptimal.

Lipid abnormalities

Serum lipids, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides increased in subjects receiving TCZ. Consults were obtained on this issue from the Division of Cardio-Renal Products and the Division of Metabolic and Endocrine Products. Below is a table of lipid changes obtained from the consult from the Division of Metabolic and Endocrine Products (Dr. Craig's, Page 3).

Table 44 Baseline (SD) and Week 14 Lipid Parameters – Double-blind Controlled Studies

	TCZ 8 mg/kg +DMARD N = 1467		TCZ 4 mg/kg + DMARD N = 714		Placebo + DMARD N = 1068		TCZ 8 mg/kg N = 260		MTX N = 253	
	BL	14 wks	BL	14 wks	BL	14 wks	BL	14 wks	BL	14 wks
Total cholesterol (mg/dL)	199	230	195	226	199	199	199	238	193	195
LDL (mg/dL)	114	137	114	133	114	115	115	144	114	117
HDL (mg/dL)	57	62	57	62	57	57	56	60	53	55
Triglycerides (mg/dL)	129	159	123	163	129	144	133	171	131	129

Week 14 is used in this analysis because it is the last fasting assessment prior to patients being eligible for escape therapy. These are patients with fasting samples at baseline.

Dr. Craig has also summarized changes of LDL:

- *At Week 24(source-Roche's Slide P105):*

TCZ 8 mg/kg: 22% increase in LDL-C (difference of 25 mg/dL or 0.7 mmol/L)
TCZ 8 mg/kg +DMARD: 17% increase in LDL-C (difference of 20 mg/dL or 0.5 mmol/L)
TCZ 4 mg/kg +DMARD: 11% increase in LDL-C (difference of 13 mg/dL or 0.3 mmol/L)
Placebo +DMARD: 3% increase in LDL-C (difference of 3 mg/dL or 0.08 mmol/L)
MTX: 4% increase in LDL-C (difference of 4 mg/dL or 0.1 mmol/L)

In the double-blind studies, serum LDL increased from < 130 mg/dL at baseline to ≥ 130 mg/dL at the last observation in **23%** of patients in the tocilizumab 8 mg/kg group, **22%** of patients treated with 8 mg/kg tocilizumab + DMARD, **15%** of patients treated with 4 mg/kg tocilizumab + DMARD, **9%** of patients treated with DMARDs, and **11%** of patients in the MTX group.

Serum LDL increased from < 160 mg/dL to above 160 mg/dL in **17%** of patients on tocilizumab 8 mg/kg, **13%** of those treated with 8 mg tocilizumab + DMARD, **11%** of those treated with 4 mg tocilizumab + DMARD, **4%** of patients treated with DMARDs, and **7%** of patients in the MTX group.

The changes demonstrated above are significant enough that they could potentially change an individual patient's risk category (i.e. increases in levels above 130 mg/dl or 160 mg/dl). So the issue becomes whether drug associated dyslipidemia increases would result in an increase risk for cardiovascular disease. This is particularly important in the population of RA patients as their disease places them at higher CV risk compared to non-RA populations. As noted above, while TCZ increased both HDL and LDL, the LDL was disproportionately increased such that the LDL/HDL ratio increases. Further complicating any prediction regarding what this may do to a patient's cardiac risk is that TCZ has profound lowering effects on CRP (table 12 above).

While we do use LDL as a surrogate for risk and base our treatment for hypercholesterolemia on reductions of LDL levels, there is no evidence regarding risk changes with drug induced dyslipidemia or any data regarding what level of elevation may be important. As the consult from the Division of Cardio-Renal Drug Products (Dr. Targum) points out, hydrochlorothiazide causes increases in cholesterol and triglycerides, yet also demonstrates benefit for targeted patients (hypertensives). Conversely, torcetrapib has an HDL raising effect, but had a detrimental effect on cardiovascular outcomes.

Exploration of the database for this application did not reveal any disproportionate CV events between TCZ arms and non-TCZ arms, however, there were very few events and limited exposure times. The consultant divisions concluded that the number and duration of patient exposure was inadequate to accurately define TCZ's cardiovascular risk profile, and the only way for a definitive answer would be a properly designed outcome study, if such a study is feasible. I agree with this assessment.

Demyelinating disorders

As Dr. Rappaport documents, there were three cases of central demyelinating events, two of which were probably multiple sclerosis. The third was diagnosed as leukoencephalopathy (negative w/u for PML) which has been reported with other immunosuppressive agents (MTX). These types of cases have been seen in other biologic development programs (TNF

inhibitors). At present we do not know what the background rate is such that we cannot tell if these cases demonstrate increased risks compared to other drugs.

2. Conclusions and Recommendations

TCZ has demonstrated efficacy for the 4 mg/kg and 8 mg/kg dose in subjects with incomplete response to MTX. In addition, TCZ at 8 mg/kg demonstrated that it is non-inferior (and may be superior) to MTX. The 8 mg/kg dose may have incremental improvement over the 4 mg/kg dose.

TCZ has also demonstrated several safety concerns many of which seem dose related.

Based on the proven efficacy of both doses, with several safety concerns that are as yet unresolved but seem to be dose related, I would advocate that if this application should ever lead to approval, both the 4 mg/kg and 8 mg/kg doses should be approved with patients initiating therapy on 4 mg/kg. This would allow clinicians the flexibility to titrate those patients that do not have an adequate response to 4 mg/kg up to 8 mg/kg, and also allow for down titration, and therefore potentially less risk, for those patients that do not get an incremental improvement in symptoms with higher dose. This would also allow for those patients that have an adverse event at 8 mg/kg to decrease their dose. The labeling should clearly reflect our concerns with the issues discussed above and we should communicate that patients at baseline risk for GI perforation should be treated only after other therapies have failed and then at the lowest effective dose.

Dr. Okada has in her review a summary table that gives some indication of the risk and benefits in terms of number-needed-to-treat and number-needed-to-harm (Page 7).

Table 6: Risk-Benefit Overview

Risk-Benefit Overview		
Clinical Activity	Proportion Responding	Number Needed to Treat
ACR20	58%	~3
ACR50	36%	~4
ACR70	18%	~7
Risks	Frequency	Number Needed to Harm
Serious Infection	5.7 per 100 pt-yrs	~56
Malignancy	1.5 per 100 pt-yrs	∞
GI Perforations	0.2 per 100 pt-yrs	~385
Demyelinating AE	.05 per 100 pt-yrs	n.d.[a]
Liver enzyme abnormalities[b]	18 per 100 pt-yrs	~7
Lipid lowering agent starts	2.8 per 100 pt-yrs	∞

Data presented pertains to TCZ 8 mg/kg + DMARD group

NNT/NNH calculations based on comparison with placebo + DMARD, controlled period, exposure adjusted

a) not determinable-one event occurred during a placebo-controlled period, but tx remains blinded

b) based on most common "marked abnormality" of elevated ALT; no clinical hepatotoxicity events noted

This table does help to remind, that this drug is very effective, and for the most part, the adverse events are very rare. As such, it would probably be an important addition to the armamentarium of drugs used to treat RA. I think it would be important to allow clinicians to use this drug, but perhaps to control that use until more safety information is available. As such, should this drug remediate the CR issues such that it can be approved, I believe that the indication, due to all the uncertainties that still exist and until we have more safety data, should reflects that TCZ be used with moderately to severely active RA in those who have had inadequate response to DMARDs and TNF inhibitors. This would allow access for the drug, is consistent with how we have approached other biological agents for RA in the past, but should limit exposure until further safety information is generated.

I believe the potential for cardiovascular risk needs further evaluation and we will need to have internal discussions to evaluate the feasibility of a long-term outcome study in RA patients. We have certainly made such request for other agents such as those used in the treatment of diabetes and for non-steroidal analgesic agents (NSAIDS). I am struck how the treatment of RA has some parallels to the treatment of HIV. Both are devastating diseases and both had lacked effective therapies until the recent past. With the first few therapies for HIV, we were willing to tolerate a lot of unknowns with safety as we were desperate for therapies. But now, due to many effective therapies and the lengthening of the life span of those infected with HIV such that it is now considered a chronic disease, we are demanding more certainty and safety data with marketed and to be marketed drugs. I believe that this approach should also apply to RA biological therapy. We now have many very effective therapies for this devastating disease such that we should not hesitate to require more safety information if we have a concerning safety signal.

I agree with Dr. Rappaport that a REMS is necessary and should include a MedGuide and the sponsor should be responsible in ensuring some level of successful laboratory monitoring for abnormal hepatic, hematologic and lipid parameters until we have more experience with the safety profile of TCZ. Since this medication, for the most part and due to the population it will be used to treat, will be limited only to infusion centers and only by specialists, I believe that it is possible, and the sponsor should be required, to provide mandatory prescriber and center training including a checklist to be completed by the infusion center staff. However, in an effort to not place such a burden that the medication will not get to those with need, I do not think that product access has to be linked to completion of training for product access. I believe this is appropriate as it reflects that we have uncertainties that we want to better define and have need for more data, as opposed to mitigating well-defined safety risks.

For this cycle, I recommend a CR action until the pre-clinical and manufacturing concerns are remediated. Upon resubmission, the sponsor should submit a complete REMS program to address the concerns outlined.

Cross-Discipline Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date: August 1, 2008

To: File, BLA 125276/0

From: Jeffrey Siegel, M.D. Jeffrey N. Siegel 8/1/08
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: BLA 125276/0
Actemra® (Tocilizumab)
Hoffman-La Roche
Proposed indication: Moderately to Severely Active RA

TABLE OF CONTENTS

1. Introduction to Review

Hoffman-La Roche is submitting this biologic licensing application (BLA) seeking the approval of tocilizumab for the treatment of patients with moderately to severely active rheumatoid arthritis (RA). Tocilizumab is a monoclonal antibody of the IgG1 subclass that binds to the interleukin-6 (IL-6) receptor, thereby inhibiting the biologic activity of IL-6. Interleukin-6 is a cytokine that is an important mediator of inflammation, including the production of acute phase reactants. It also acts as a growth factor for certain cells and regulates cells of the immune system. Hoffman-La Roche conducted an extensive Phase 3 clinical development program, including five Phase 3 trials, exploring the efficacy and safety of tocilizumab in early and established RA, as monotherapy and in combination with methotrexate (MTX) and with other disease-modifying anti-rheumatic drugs (DMARD's). They propose administration of tocilizumab as an intravenous infusion given over 1 hour at a dose of 8 mg/kg IV every 4 weeks. Overall, the safety database in the RA clinical development program consisted of a total of 3778 patients treated with tocilizumab, including 3474 treated for 3 months or longer, 3183 treated for 6 months or longer and 2121 treated for 12 months or longer.. Of the patients treated with tocilizumab, most (3242 of 3778) were treated with the 8 mg/kg dose.

During the review of this application, important issues arose regarding pharmacology/toxicology, CMC and clinical safety. The pharmacology/toxicology issues concerned whether the applicant had adequately addressed the need for reproductive toxicology studies and carcinogenicity studies. The CMC issues concerned deficiencies noted on inspection of a manufacturing site and were not fully resolved at the time of writing of this review. The review of the clinical trials revealed several safety issues, including a higher rate of serious infections, liver enzyme elevations, abnormal hematology parameters, lipid abnormalities, the occurrence of gastrointestinal perforation events and demyelinating events. This memo will review the regulatory background for this application, the evidence supporting efficacy and safety of tocilizumab in RA and key findings in other disciplines and will carefully consider the overall risk/benefit relationship of tocilizumab in RA.

2. Background – Regulatory history

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition that primarily affects the joints but can also affect other organs. Active RA is associated with pain and physical impairment. If left untreated or inadequately treated RA leads to progressive damage to joints with subsequent disability and the need for joint replacement. The FDA Guidance for Industry on clinical development programs for RA (RA guidance document) describes the types of clinical trials needed for approval of products for RA. The basic claim usually assessed in clinical trials for approval is improvement in signs and symptoms as measured by an accepted composite index such as the ACR 20 (American College of Rheumatology 20). Claims describing additional benefits that can be assessed in clinical trials include improvement in physical function, major clinical response, inhibition of progression of structural damage, complete clinical response and remission.

Following completion of their Phase 2 clinical development program for tocilizumab in RA, Hoffman-La Roche met with the Agency in an End of Phase 2 meeting. At that meeting agreement was reached on a range of issues regarding the Phase 3 program, including endpoints to support a signs and symptoms claim, a claim of inhibition of progression of structural damage and improvement in physical function. The Agency provided recommendations on the statistical analytic plan, including the use of sequential procedures to avoid multiplicity issues with the use of several endpoints in the clinical trials. The Agency agreed in principle to use of a non-inferiority design for the head-to-head trial against methotrexate (MTX) but recommended inclusion of a small placebo arm to provide internal evidence for the effect size of the active control arm and specified that Hoffman-La Roche should provide a rationale for the 12% non-inferiority margin.

3. CMC/Microbiology/Device

3.1. General product quality considerations

The product review team has completed their review and determined that there are no issues that would prevent an approval, including reviews of drug substance, drug product, and release specifications. The PK assays, potency assay and immunogenicity assays were reviewed and judged to be well-validated. Importantly, tocilizumab was shown to interfere with binding of IL-6 to the IL-6 receptor but to have no effector function.

3.2. Facilities review/inspection

When the facilities inspection team carried out an inspection of the Utsunomiya manufacturing facility in Japan they uncovered major deficiencies. These deficiencies include, but are not limited to, use of ——— in the qualification of tank and bioreactor equipment, insect infestation and inadequate facility cleaning and disinfection. They communicated these deficiencies to Hoffman-La Roche and received a response. At the time of this review the response from the applicant was still under review. If these issues cannot be addressed before the action date of this submission the license application cannot be approved. b(4)

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Ashoke Mukherjee, determined that the studies submitted were acceptable but expressed concern regarding the lack of carcinogenicity studies and the lack of reproductive toxicology seg 3 studies.

4.1. Carcinogenicity and Reproductive Toxicology

Regarding the carcinogenicity studies the applicant provided a variety of arguments for why carcinogenicity studies were not needed and were not feasible. In general, the literature suggests that IL-6 has predominantly pro-proliferative effects and can serve as a growth factor for tumors. Thus, blocking IL-6 would not be expected to promote tumors. The applicant argues that carcinogenicity studies are not feasible because tocilizumab does not bind IL-6R in other species. Dr. Mukherjee found the arguments unconvincing. While he acknowledges that tocilizumab does not bind to the IL-6R in other species he

recommends the applicant develop a species-specific monoclonal antibody and conduct carcinogenicity studies using that monoclonal. At the present time the Pharmacology/Toxicology supervisor, Dr. Dan Mellon, is in the process of completing his review. At the time of writing of this review Dr. Mellon's stated that the Agency had previously agreed that carcinogenicity studies and seg 3 studies would not be needed for approval of tocilizumab. Dr. Mellon related that he would not recommend that the applicant be required to conduct carcinogenicity studies or seg 3 studies prior to approval. He is still considering whether seg 3 studies should be required as a postmarketing commitment.

At this point in time there are extensive studies in humans extending out to several years in duration that have not shown evidence of an increased risk of malignancies. Therefore, additional animal studies of carcinogenicity may be of limited value.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations

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). PK was similar in patients with RA.

A population PK analysis demonstrated a non-linear component of clearance at low concentrations of tocilizumab and a linear component at higher concentrations. The non-linear component is more important at the 4 mg/kg dose than at the 8 mg/kg dose. Linear clearance increased with increasing body weight.

5.2. Drug-drug interactions

Since IgG antibodies are not metabolized by P450 enzymes, direct pharmacokinetic interaction via the CYP pathway is not expected between tocilizumab and small molecules. POP-PK analysis showed no effect on tocilizumab PK of commonly coadministered drugs in RA patients including methrotrexate, leflunomide, NSAIDs (e.g., naproxen, ibuprofen, celecorxib, diclofenac, meloxicam) and analgesics (e.g., acetaminophen, codeine, tramadol). However, there is the possibility of indirect effects of tocilizumab on P450 enzymes. The cytokine IL-6 decreases P450 activity, suggesting that disinhibition of IL-6 by tocilizumab could increase P450 activity. In vitro studies with human hepatocytes demonstrated that tocilizumab could indeed prevent the IL-6 mediated reduction in P450 enzyme activity. Consistent with this finding, an in vivo study showed that co-administration of tocilizumab 8 mg/kg resulted in a decrease in exposure of omeprazole (~50%) in CYP2C19 extensive metabolizers indicating reversal of down-regulation of CYP2C19.

Based on these findings the Clinical Pharmacology reviewer, Lei Zhang, recommends language in the package insert informing prescribers about the potential for changes in

blood levels of coadministered products that are P450 substrates with a narrow therapeutic index

5.3. Pathway of Elimination

For antibodies such as tocilizumab, two types of pathways mediate elimination mechanisms: a nonspecific linear clearance by the reticuloendothelial system and an antigen-mediated saturable clearance.

5.4. Demographic interactions/special populations

POP-PK analyses demonstrated no effect of age, gender, race or ethnicity on the PK of tocilizumab in adult RA patients. No information was submitted on PK in children. The applicant has requested a deferral for pediatric studies.

5.5. Thorough QT study or other QT assessment

The effects of tocilizumab on QT were not formally assessed as biologic products like tocilizumab are generally not expected to interact with cardiac ion channels.

5.6. Notable issues

None.

6. Clinical/Statistical

6.1. General Discussion

The applicant conducted five Phase 3 trials of efficacy and safety of tocilizumab in patients with RA. These trials included patients with early RA and established RA. They studied tocilizumab monotherapy and tocilizumab in combination with MTX and with a variety of other disease-modifying anti-rheumatic drugs (DMARD's). In this application, the applicant submitted data on signs and symptoms. In a subsequent submission they plan to submit data on radiographic progression. In general, the applicant followed advice provided by the Agency in the End of Phase 2 meeting on the design and analysis of the clinical trials.

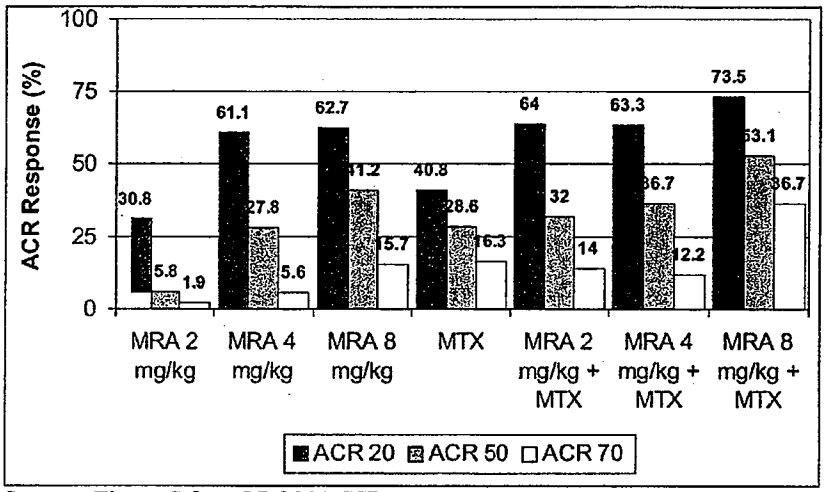
6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The applicant decided on a dose based on a dose-finding study conducted by Chugai Pharmaceuticals. This randomized, controlled, 20-week trial (Study LRO301), studied doses of 2, 4 and 8 mg/kg every 4 weeks with or without placebo. The results of this study (Figure 1, this and other figures and tables in this section copied from the review of Dr. Sarah Okada) showed higher ACR 20 responses with the 4 and 8 mg/kg doses than the 2 mg/kg dose. Higher level responses (ACR 50 and ACR 70 responses) were more

frequent with the 8 mg/kg dose than the 4 mg/kg dose. Based on these data, Hoffman-La Roche selected the 8 mg/kg dose as the main dose for most of the Phase 3 trials.

Figure 1: Proportion of ACR Responders by Treatment Group, Study LRO301



Source: Figure C from LRO301 CSR

At the July 29, 2008 meeting of the Arthritis Advisory Committee Hoffman-La Roche showed a slide of the individual components of the ACR response criteria in a trial comparing 4 mg/kg to 8 mg/kg to placebo. Dr. David Felson, a panel member, pointed out that most of the individual components showed little difference between 4 mg/kg and 8 mg/kg and that the component driving the differences between 4 and 8 mg/kg was primarily the laboratory component, the CRP, which showed large differences between 4 and 8 mg/kg. He argued that therefore the correct initial dose for DMARD incomplete responders was 4 mg/kg. He acknowledged that in other patient groups, e.g., TNF blocker incomplete responders, that 8 mg/kg provided better efficacy than 4 mg/kg. Other members of the panel agreed with Dr. Felson.

Is 4 mg/kg preferable as a recommended starting dose than 8 mg/kg? Not necessarily. Although 4 mg/kg and 8 mg/kg provide similar effects on symptoms 8 mg/kg does achieve somewhat greater improvement in each of the components of the ACR response criteria (Table 1). Although the component with the largest difference is acute phase reactants, these acute phase reactants are a measure of inflammation so this finding should not simply be discounted. In addition, in certain population, e.g., patients who have previously shown an inadequate response to a TNF blocker the 8 mg/kg dose provided good responses while the effects of 4 mg/kg were more modest. The effects of the 4 mg/kg dose is unknown in the setting of monotherapy since only the 8 mg/kg dose was studied in this setting. Safety results for 4 mg/kg and 8 mg/kg are generally similar. Finally, there is the issue of cardiovascular effects of tocilizumab. As will be described in further detail below tocilizumab is associated with an increase in LDL levels, a lipid associated with increased cardiovascular risk. Although no signal for increased cardiovascular events were seen in the tocilizumab safety database that may be because an increase in risk contributed by increased LDL levels is counterbalanced by a reduction

in risk due to decreased CRP levels. Since most of the data, especially the long-term open-label data, involve the 8 mg/kg dose recommending a 4 mg/kg dose would mean exposing patients to a dose that had not been as extensively studied. In summary, while efficacy for most signs and symptoms of RA were similar between the 4 and 8 mg/kg doses the 8 mg/kg dose achieved somewhat better results with similar safety. Arguments can be made for and against recommending the 4 mg/kg dose as a starting dose.

Table 1: Mean Change in ACR Components, Baseline to Week 24

Summary of Change in ACR Components, baseline to Week 24, by Trial and Treatment

RA Population:	DMARD Inadequate			DMARD Inadequate			Early RA		TNF Inadequate			DMARD Inadeq.	
	WA17822			WA17823			WA17824		WA18062			WA18063	
	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	MTX n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 8 n (%)
ITT Population (PP for WA17824)	204	213	205	393	399	398	259	265	158	161	170	413	803
SJC (66 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 264	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-4.3	-8.5	-10.5	-2.5	-7.4	-8.5	-7.8	-11.7	-0.5	-6.8	-7.8	-4.9	-10.3
Adjusted Mean Diff.	-	-4.2	-6.2	-	-4.8	-5.9	-	-3.9	-	-6.2	-7.2	-	-5.5
95% CI of Difference	-	(-6.1,-2.3)	(-8.1,-4.2)	-	(-6.1,-3.5)	(-7.2,-4.6)	-	(-5.7,-2.0)	-	(-9.0,-3.5)	(-9.9,-4.5)	-	(-6.7,-4.3)
TJC (68 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 264	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-7.4	-14.5	-17.1	-4.9	-12.1	-14.0	-13.5	-17.1	0.3	-10.5	-14.8	-8.5	-15.7
Adjusted Mean Diff.	-	-7.0	-9.6	-	-7.2	-9.1	-	-3.6	-	-10.8	-15.1	-	-7.1
95% CI of Difference	-	(-10.0,-4.1)	(-12.6,-6.7)	-	(-9.2,-5.2)	(-11.1,-7.1)	-	(-6.3,-1.0)	-	(-14.6,-7.1)	(-18.8,-11.4)	-	(-8.9,-5.4)
Patient Global (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 316	n = 230	n = 242	n = 61	n = 108	n = 129	n = 322	n = 729
Adjusted Mean*	-17.8	-28.8	-32.7	-18.4	-24.9	-25.7	-29.5	-33.5	-15.4	-25.4	-32.8	-16.3	-33.2
Adjusted Mean Diff.	-	-10.9	-14.9	-	-6.5	-7.3	-	-4.1	-	-10.0	-17.4	-	-16.8
95% CI of Difference	-	(-17.1,-4.8)	(-20.9,-8.9)	-	(-11.4,-1.6)	(-12.1,-2.4)	-	(-9.3,+1.2)	-	(-20.3,+0.3)	(-27.8,-7.0)	-	(-20.5,-13.2)
Physician Global (mm)	n = 123	n = 158	n = 173	n = 214	n = 307	n = 320	n = 229	n = 242	n = 61	n = 105	n = 127	n = 322	n = 733
Adjusted Mean*	-32.7	-38.3	-41.6	-28.2	-34.0	-38.3	-31.5	-41.6	-20.0	-30.5	-38.2	-21.6	-35.9
Adjusted Mean Diff.	-	-5.6	-9.0	-	-5.8	-10.1	-	-10.1	-	-10.5	-18.2	-	-14.4
95% CI of Difference	-	(-10.5,-0.8)	(-13.8,-4.2)	-	(-9.6,-1.9)	(-14.0,-6.2)	-	(-14.2,-6.0)	-	(-18.6,-2.5)	(-26.3,-10.0)	-	(-17.3,-11.4)
Patient's Pain (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 317	n = 231	n = 242	n = 61	n = 105	n = 129	n = 322	n = 730
Adjusted Mean*	-14.0	-25.0	-29.8	-13.1	-19.3	-22.2	-29.5	-31.5	-8.6	-21.0	-32.5	-12.8	-29.9
Adjusted Mean Diff.	-	-11.0	-15.8	-	-6.2	-9.1	-	-2.0	-	-12.4	-23.9	-	-17.1
95% CI of Difference	-	(-17.0,-5.0)	(-21.7,-9.9)	-	(-10.9,-1.5)	(-13.9,-4.4)	-	(-7.1,+3.1)	-	(-22.1,-2.6)	(-33.7,-14.1)	-	(-20.8,-13.4)
CRP (mg/dL)	n = 122	n = 157	n = 172	n = 214	n = 308	n = 321	n = 230	n = 242	n = 63	n = 106	n = 129	n = 324	n = 727
Adjusted Mean*	-0.35	-1.66	-2.51	-0.14	-0.70	-1.89	-1.81	-2.85	-0.06	-1.40	-2.58	-0.27	-2.19
Adjusted Mean Diff.	-	-1.30	-2.16	-	-0.57	-1.76	-	-1.04	-	-1.34	-2.52	-	-1.93
95% CI of Difference	-	(-2.01,-0.59)	(-2.86,-1.46)	-	(-1.00,-0.13)	(-2.19,-1.32)	-	(-1.67,-0.41)	-	(-2.54,-0.15)	(-3.72,-1.32)	-	(-2.32,-1.54)
ESR (mm/hr)	n = 122	n = 157	n = 174	n = 211	n = 304	n = 318	n = 229	n = 240	n = 62	n = 107	n = 129	n = 325	n = 732
Adjusted Mean*	-7.1	-25.5	-39.5	-7.1	-19.4	-34.6	-15.1	-37.2	-3.0	-19.7	-37.2	-4.7	-35.6
Adjusted Mean Diff.	-	-18.3	-32.3	-	-12.3	-27.5	-	-22.1	-	-16.7	-34.2	-	-30.9
95% CI of Difference	-	(-24.3,-12.4)	(-38.2,-26.5)	-	(-16.7,-8.0)	(-31.9,-23.2)	-	(-27.2,-17.1)	-	(-25.4,-8.1)	(-43.0,-25.5)	-	(-34.2,-27.6)
HAQ-DI	n = 101	n = 126	n = 141	n = 197	n = 292	n = 301	n = 230	n = 243	n = 62	n = 106	n = 130	n = 322	n = 724
Adjusted Mean*	-0.34	-0.52	-0.55	-0.30	-0.41	-0.50	-0.48	-0.70	-0.05	-0.31	-0.39	-0.20	-0.47
Adjusted Mean Diff.	-	-0.18	-0.21	-	-0.10	-0.19	-	-0.22	-	-0.25	-0.34	-	-0.27
95% CI of Difference	-	(-0.34,-0.02)	(-0.37,-0.05)	-	(-0.20,-0.00)	(-0.30,-0.09)	-	(-0.22,-0.34)	-	(-0.42,-0.09)	(-0.51,-0.17)	-	(-0.34,-0.20)

*ANOVA

LOCF used for tender and swollen joint counts if missing or patient entered escape

No imputation used for missing HAQ score, CRP, ESR, and VAS assessments

Adapted from Tables 23 and 29 of WA17822 CSR, Tables 22 and 27 of WA17823 CSR, Tables 32 and 38 of WA17824 CSR, Tables 33 and 38 of WA18062 CSR, and Tables 25 and 30 of WA18063 CSR

6.2.2. Phase 3/ clinical studies essential to regulatory decision

The applicant submitted results from five Phase 3 trials of tocilizumab in patients with moderately to severely active RA diagnosed by ACR criteria. Studies WA17822 and WA17823 studied the addition of tocilizumab to background stable MTX. Study WA18062 enrolled a more refractory patient population who had previously had an inadequate response to TNF blockers. Study WA18063 was a study intended to represent how tocilizumab is likely to be prescribed if it is approved, namely by adding it to whatever background DMARD's the patient was previously receiving. Of note, Study WA18063 excluded concomitant biologics. Finally, Study WA17824 enrolled patients

with less longstanding RA who were not receiving a DMARD at the time of enrollment. Study WA17824 was a head-to-head trial comparing tocilizumab to MTX. It utilized an aggressive dose escalation strategy where MTX was initiated at 7.5 mg/wk then increased to 20 mg/kg by week 8 so long as the patient continued to have active disease. Stable NSAID's and corticosteroids were allowed (prednisone equivalent dose 10 mg/d or less)

The primary endpoint for each of the studies was the ACR 20 response at week 24. All were designed as superiority studies, except for Study 17824, which was designed as a non-inferiority study. Analyses for the superiority trials utilized the intent-to-treat principle. Non-responder imputation was used for missing data. The non-inferiority margin for StudyWA17824 was specified as 12%. The statistical analytic plan specified that if the non-inferiority endpoint was established that the superiority of tocilizumab to MTX could then be tested.

In general, the patient populations enrolled were typical of the general RA population. They had moderately to severely active disease. Most were female and Caucasian. Approximately three-quarters were rheumatoid factor-positive. In general, most (over 80% in all trials; 90% or more in most) patients completed 24 weeks of study (Table 2). Early escape was allowed for poor responders to study treatment. Early escape was more frequent among patients randomized to placebo than to tocilizumab treatment. Discontinuations due to adverse events were somewhat more common in the tocilizumab arms compared to the placebo arms. Dropouts due to lack of efficacy were more frequent in the placebo control arms than with active treatment.

Table 2: Patient Disposition

Summary of Patient Disposition by Trial and Treatment

RA Population:	DMARD Inadequate			DMARD Inadequate			Early RA			TNF Inadequate			DMARD Inadeq.	
	WA17822			WA17823			WA17824			WA18062			WA18063	
	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo* n (%)	MTX n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 8 n (%)
ITT Population	204	213	205	393	399	398	101	284	288	158	161	170	413	803
Completed	189 (93)	185 (87)	191 (93)	356 (91)	373 (93)	366 (92)	82 (81)	262 (92)	268 (93)	127 (80)	138 (86)	152 (89)	370 (90)	751 (94)
Entered Escape	68 (33)	31 (15)	19 (9)	150 (38)	67 (17)	41 (10)	14 (14)	11 (4)	7 (2)	66 (42)	31 (19)	20 (12)	45 (11)	19 (2)
Total discontinuations	15 (7)	28 (13)	14 (7)	36 (9)	26 (7)	33 (8)	19 (19)	22 (8)	20 (7)	33 (21)	25 (16)	23 (14)	43 (10)	53 (7)
Discontinuation due to AEs	8 (4)	16 (8)	12 (6)	12 (3)	16 (4)	22 (6)	5 (5)	11 (4)	9 (3)	10 (6)	10 (6)	11 (6)	8 (2)	32 (4)
SAEs (other than death)	1	5	4	4	7	3	0	3	2	5	2	3	3	13
Deaths	1	0	0	1	0	0	0	1	3	0	0	0	2	2
Other AE	6	11	8	7	9	19	5	7	4	5	8	8	3	17
Other withdrawals	7 (3)	12 (6)	2 (1)	24 (6)	10 (3)	11 (3)	14 (14)	11 (4)	11 (4)	23 (15)	15 (9)	12 (7)	35 (8)	21 (3)
Insufficient treatment effect	4	3	0	13	2	1	4	3	1	19	6	4	15	3
Protocol violation	1	1	0	2	0	0	2	0	0	0	2	2	3	0
Lost to follow-up	0	1	0	1	1	0	4	1	4	0	4	1	2	2
Patient choice	2	6	1	8	7	9	3	7	6	4	2	4	13	15
Other	0	1	1	1	0	1	1	0	0	0	1	1	2	1

*Placebo controlled substudy

Sources: Fig 2, Tables 6&7; pg 170-171 | Fig 2, Tables 6,7,51; pg 164-165 | Fig 3, Tables 6&72 sections 3.1.1 & 7.3 | Fig 2, Tables 5&6; pg 192 | Fig 2, Table 5 section 3.5.2.4

As shown in Table 3, the groups of patients treated with tocilizumab achieved statistically significantly greater improvement in ACR 20 response rates than patients receiving placebo in each of the four superiority trials. For the three trials that added tocilizumab to background MTX or other DMARD's the ACR 20 response rates at week 24 were approximately 55-60% compared to placebo control responses of approximately 25%. In patients with a prior incomplete response to prior TNF blocker therapy a greater proportion of patients treated with tocilizumab 8 mg/kg achieved an ACR 20 response than patients receiving placebo (50% vs. 10%). However, patients in that study who

received tocilizumab 4 mg/kg had a more modest response (30% ACR 20 responders). In the head-to-head trial comparing tocilizumab 8 mg/kg to MTX in MTX-naïve subjects the non-inferiority endpoint was achieved. As per the statistical analytic plan, the tocilizumab group was then compared to the MTX group in a superiority analysis. Tocilizumab 8 mg/kg was found to be statistically significantly superior to MTX (ACR 20 responses 70% vs. 52%).

Key findings from the primary and secondary endpoints were confirmed by the FDA statistical reviewer, Joan Buenconsejo. Sensitivity analyses conducted by the applicant and independent analyses conducted by the Agency confirmed that results were not due to the manner of imputing missing data. Subgroup analyses examining patients by baseline demographics and by baseline disease characteristics did not identify any subgroups of patients who did not demonstrate a treatment effect of tocilizumab. Of note, there was an apparent relationship between the baseline level of CRP and the likelihood of response, with patients in the lowest CRP stratum (<0.3 mg/dL) showing a 47% response rate and patients with the highest CRP levels (>10 mg/dL) demonstrating a 70% response (see Table 10 from Dr. Sarah Okada's review). In general, the results of the secondary endpoints were supportive of the results of the primary analyses.

Table 3: Proportion of ACR20/50/70 Responders at Week 24

Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment (ITT Populations)					
Study	**Pbo + DMARD****	**TCZ 4mg/kg + DMARD****	**TCZ 8mg/kg + DMARD****	**p-value (4 mg/kg)**	**p-value (8 mg/kg)**
Patients with incomplete response to MTX or other DMARDs					
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
WA18063	(n=413)		(n=803)		
ACR20	24		61		**<0.0001**
ACR50	9		38		<0.0001
ACR70	3		20		<0.0001
Patients with incomplete response to prior TNF inhibitor treatment					
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
MTX naive/Early RA patients					
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 for primary analysis population

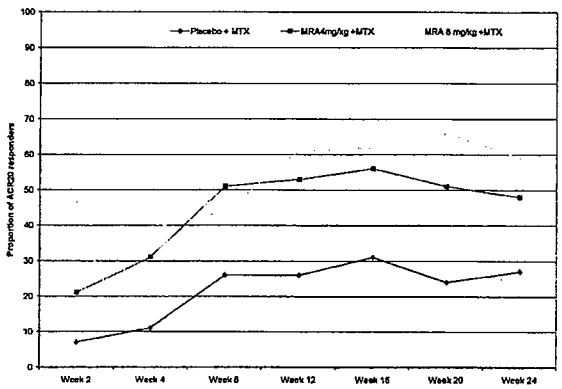
**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 19 of WA17822 CSR, Tables 17 & 18 of WA17823 CSR, Tables 17 & 22 of WA17824 CSR
Tables 21 & 23 of WA18062 CSR, and Tables 17 & 20 of WA18063 CSR

Although ACR 20 responses are considered clinically meaningful, higher level responses are particularly important to patients and health care providers. Patients treated with tocilizumab had higher level responses (ACR50 and ACR 70) more frequently than controls in a dose-dependent manner. As noted above (section 6.2.1) much but not all of the higher response rates were attributable to a much larger reduction in CRP levels with the 8 mg/kg dose than with the 4 mg/kg dose. Overall, improvement in all the components of the ACR responses was observed (Table 1) so the improvements were not due simply to improvement in one or a few components of the ACR response criteria.

ACR 20 responses were observed as early as week 2 and were maintained to 24 weeks (Figure 2).

Figure 2: Study WA17822: ACR 20 responders by week



In summary, the five Phase 3 studies demonstrated efficacy of tocilizumab for treating the signs and symptoms of RA. Clinical benefit was observed in DMARD-naïve patients, in patients with an inadequate response to conventional DMARDs and in patients who had previously had an inadequate response to, or were intolerant of, a TNF blocker.

6.2.3. Other efficacy studies

None

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical review, Dr. Sarah Okada, concluded that the studies demonstrated efficacy of tocilizumab in the treatment of RA. The biostatistics reviewer, Dr. Buenconsejo concluded that the studies provided statistical support in favor of tocilizumab 8 mg/kg either as a monotherapy or a combination therapy. Regarding the choice of dose Dr. Buenconsejo concluded that there was evidence that tocilizumab 4 mg/kg in combination with MTX therapy is associated with reduction in signs and symptoms of RA after 24 weeks of therapy. Although there was no direct statistical comparison, there is some evidence that the effect was consistently lower than that of the TCZ 8 mg/kg group.

6.2.5. Pediatric use/PREA waivers/deferrals

The applicant has requested a deferral for patients age 2-17 with polyarticular juvenile idiopathic arthritis (JIA), and a waiver for children 0-2. The applicant has already discussed details of their proposed Phase 3 program in polyarticular JIA with the Agency. This study is planned to commence enrollment in the 4th quarter of 2008, with submission of the final study report planned for 2012. The applicant's proposed plan for studies in children appears adequate.

6.2.6. Discussion of notable efficacy issues

There are no notable efficacy issues.

6.3. Safety

6.3.1. General safety considerations

Due to the association of certain serious but uncommon adverse events with immunosuppressive agents, in order to adequately assess safety it is necessary to have a safety database that is larger than may be required for nonimmunosuppressive agents. In addition events may become apparent only with long durations of exposure. Consequently, the expected size of the safety database is greater than the minimum guidelines recommended in the ICH E1 guidance document. Generally for immunosuppressive products for RA the Division expects data on at least 1000-1500 patients treated for at least one year.

The safety database submitted in support of tocilizumab consists of the clinical trials in RA (Table 4), clinical trials in other indications including multicentric Castleman's disease and systemic JIA and postmarketing data from Japan, where tocilizumab is approved and marketed for the treatment of multicentric Castleman's disease. The safety database in RA consists of data from randomized, controlled trials as well as data from long-term open-label treatment studies designed to study long-term safety of tocilizumab. Overall, safety data are available on 3778 patients with RA treated for any period of time. A total of 3474 patients have received tocilizumab for at least 6 months, 2121 patients for at least one year. A total of 640 patients have received tocilizumab for 2 years or longer. Most of the exposure has been to tocilizumab 8 mg/kg, although a total of 1181 patients have received the 4 mg/kg dose.

Table 4: Exposure to Tocilizumab

Exposure in the Roche Tocilizumab RA Pivotal Studies and Long-Term Extensions		
Population	Number of patients	Duration TCZ exposure (patient-yrs)
6 mo safety population, all TCZ	2644	1131
Pooled Long Term Extensions	2562	3685
All Exposure	3778	4142
≤3 months	*3474*	*799*
≤6 months	*3183*	*1464*
≤12 months	*2121*	*1951*
≤18 months	*1463*	*2019*
≤24 months	*640*	*1178*
≤30 months	*113*	*260*
Total exposure, TCZ 4 mg/kg	1181	435
Total exposure, TCZ 8 mg/kg	3242	3707

Source: Table 3 and 4 of 120 day safety update, data cut-off Oct. 1, 2007

Some safety concerns are expected in view of the mechanism of action of tocilizumab. Given that IL-6 and the IL-6 receptor, the targets of tocilizumab, are key mediators of inflammation and immunity tocilizumab is expected to have immunosuppressive properties. Adverse events associated with immunosuppression include an increased risk of infection, possible effects on risk of malignancy and potential effects on the propensity to develop autoimmunity. In addition, because the IL-6R is expressed in the liver there is the potential for effects on liver function. Finally, it is important to evaluate effects of adding tocilizumab to other disease-modifying agents patients may be receiving concomitantly to assess for the possibility of adverse events related to combined immunosuppression.

Exposure in the Roche Tocilizumab RA Pivotal Studies and Long-Term Extensions		
Population	Number of patients	Duration TCZ exposure (patient-yrs)
6 mo safety population, all TCZ	2644	1131
Pooled Long Term Extensions	2562	3685
All Exposure	3778	4142
≤ 3 months	*3474*	*799*
≤ 6 months	*3183*	*1464*
≤ 12 months	*2121*	*1951*
≤ 18 months	*1463*	*2019*
≤ 24 months	*640*	*1178*
≤ 30 months	*113*	*260*
Total exposure, TCZ 4 mg/kg	1181	435
Total exposure, TCZ 8 mg/kg	3242	3707

Source: Table 3 and 4 of 120 day safety update, data cut-off Oct. 1, 2007

6.3.2. Safety findings from submitted clinical trials

Because patients with an inadequate response to therapy were allowed early escape there was a greater duration of exposure of patients to tocilizumab than to placebo in the controlled trials. Therefore, analyses were conducted both on overall rates (Table 5) of adverse events (AEs) and on exposure adjusted rates (Table 6). As shown in Table 6 the proportion of patients experiencing any AE was higher with tocilizumab than with placebo control. However, the rate of AE's was not higher with tocilizumab than observed with MTX. Exposure-adjusted rates of death were not increased with tocilizumab treatment nor were the rates of malignancy. Serious adverse events were observed at similar rates with tocilizumab as in controls and did not increase with longer durations of exposure. Serious infectious events (SIEs) were more frequent with tocilizumab 8 mg/kg than with placebo (5.7 vs. 3.9 SIE per 100 pt-yrs). With longer duration of exposure to tocilizumab SIE rates decreased to a level seen with placebo controls (3.8 SIE per 100 pt-yrs). Rates of SIEs were somewhat higher with tocilizumab 8 mg/kg as with the 4 mg/kg dose (5.7 vs. 4.7 events/100 pt-yrs).

Table 5: Overview of AEs and Deaths

Overview of AEs and Deaths 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	2562
Pts with any AEs	733 (63)	220 (77)	547 (71)	1134 (72)	230 (80)	1911 (72)	2259 (88)
Deaths	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)
Pts with SAEs	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Pts with AEs leading to withdrawal	28 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Pts with AEs leading to dose modif.	84 (7)	63 (22)	103 (13)	194 (12)	56 (19)	353 (13)	884 (34)

*Includes MTX

Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population

Adapted from Table 15 of Module 2.7.4 and Table 5 of 120 day safety update

Table 6: Exposure-Adjusted Rates of SAEs, SIEs, malignancies and Deaths

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	2562
Total patient-years exposure	462	123	321	685	126	1131	3685
Deaths, n (%)	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)
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)	60 (2.3)
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6
No. with ≥1 SAE, n (%)	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Number of SAE	74	15	51	115	12	178	489
SAEs per 100 pt-yrs	16	12	16	17	10	16	13
No. with ≥1 SIE, n (%)	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)
Number of SIE	18	2	15	39	4	58	141
SIEs per 100 pt-yrs	3.9	1.6	4.7	5.7	3.2	5.1	3.8

* Includes MTX

Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population

Adapted from Tables 12, 13, 24, 27 and 38 of Module 2.7.4 Summary of Clinical Safety and source tables STae_py_mal and STrate_ae_s; and tables 4, 5, 9, 20 and stae11_sl of 120 d safety update; p.5 of Amendment 14

Overall, the major safety issues with this application are serious infections, GI perforations, laboratory abnormalities (liver enzyme elevations, hematologic abnormalities and increases in LDL levels) and demyelinating events.

With regard to serious infections, as detailed above, the rate of serious infection in the controlled trials was increased among tocilizumab-treated patients compared to controls. The rate of serious infections fell over time with longer durations of exposure to tocilizumab. The types of serious infections were similar to those seen with other commonly used immunosuppressive DMARD's in RA. Given the global nature of the clinical development program there did not appear to be an elevated risk of tuberculosis even though there were not specific requirements for screening and prophylaxis for latent tuberculosis infection. A total of two opportunistic infections were diagnosed: one case

of pneumocystis jiroveci pneumonia and one case of mycobacterium avium intracellulare pneumonia.

Cases of gastrointestinal perforation were observed in the clinical development program of tocilizumab. During the 6-month controlled period, there were 3 gastrointestinal perforation events in the TCZ 8 mg/kg treatment groups and none in the placebo or TCZ 4 mg/kg per treatment groups. Overall, GI perforations were uncommon (Table 7). Exploration of other databases of RA patients indicates that GI perforations do occur in this patient population. The rates appear somewhat higher with tocilizumab. Examination of the individual cases reveal that most patients had concomitant use of NSAID's and corticosteroids, known predisposing factors for GI perforation.

Table 7: Exposure Adjusted Incidence of GI Perforations

Exposure-Adjusted Incidence of GI Perforations in RA Patients				
	TCZ program Events	TCZ program Events/100 pt-yrs	UHC database Events/100 pt-yrs	Marketscan database Events/100 pt-yrs
Upper GI	4	0.05	0.03	0.02
Lower GI	12	0.15	0.16	0.14
Total	16	0.20	0.18	0.16

Data cut-off December 31, 2007

Sources: Tables 14 and 15 of 120 day safety update

Liver enzyme elevations were observed more frequently in tocilizumab-treated patients than in controls. The study protocol stipulated dose adjustment or suspension of dosing for liver enzyme elevations. No clinically apparent hepatic adverse events were observed in the safety database. As shown in Table 8 marked increases in liver enzymes were quite uncommon. However, there was one case that met Hy's Law criteria. This patient completed the 6 months of TCZ 8 mg/kg monotherapy with only isolated increases in total bilirubin to greater than 1x ULN and without simultaneous increase in transaminases or alkaline phosphatase. During the long-term extension study she began MTX at 20 mg weekly without the usual dose titration in addition to treatment with open-label TCZ at 8 mg/kg. After she was noted to have elevations of AST and ALT to 2x and 4x ULN and elevated total bilirubin to less than 2x ULN she stopped MTX and tocilizumab. Subsequently, AST peaked at greater than 10x ULN, ALT at greater than 16x ULN and total bilirubin at greater than 2x ULN. Liver enzymes subsequently returned to the normal range and MTX was restarted. When tocilizumab was then restarted at 4 mg/kg liver enzymes and bilirubin again rose and tocilizumab was discontinued. At the Advisory Committee representatives of Hoffman-La Roche argued that this was a case of Gilbert's syndrome. Against this diagnosis is the fact that bilirubin levels were not elevated at baseline and the fact that bilirubin levels increased in a manner temporally associated with marked elevations in AST and ALT.

In summary, treatment with tocilizumab is associated with elevations in liver enzymes. No clinical hepatotoxic events were observed. While there was a single case meeting Hy's law criteria that case was confounded by its occurrence when another hepatotoxic

agent was added to tocilizumab treatment. If tocilizumab is approved liver enzymes should be carefully monitored, especially when it is used concomitantly with a known hepatotoxic agent.

Table 8: Hepatobiliary Worst Values

Hepatobiliary Worst Values in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
		6-months pooled safety population						Long term safety population
	range	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	2562
AST (U/L)								
normal	0-40	967 (83)	201 (71)	498 (64)	902 (57)	220 (76)	1620 (61)	1319 (51)
>ULN to 3 x ULN	41-120	194 (17)	74 (26)	264 (34)	646 (41)	64 (22)	974 (37)	1176 (46)
>3 x ULN to 5 x ULN	121-200	3 (0.3)	5 (2)	8 (1)	29 (2)	1 (0.3)	38 (1)	53 (2)
>5 x ULN to 8 x ULN	201-320	-	1 (0.4)	1 (0.1)	1 (0.1)	1 (0.3)	3 (0.1)	7 (0.3)
>8 x ULN	>320	1 (0.1)	-	-	2 (0.1)	1 (0.3)	3 (0.1)	2 (0.1)
ALT (U/L)								
normal	0-55	877 (75)	172 (61)	376 (49)	714 (45)	176 (61)	1266 (48)	991 (39)
>ULN to 3 x ULN	56-165	270 (23)	95 (33)	349 (45)	763 (48)	105 (36)	1217 (46)	1370 (53)
>3 x ULN to 5 x ULN	166-275	15 (1)	11 (4)	36 (5)	80 (5)	4 (1)	120 (5)	170 (7)
>5 x ULN to 8 x ULN	276-440	1 (0.1)	2 (0.7)	10 (1)	21 (1)	1 (0.3)	32 (1)	20 (0.8)
>8 x ULN	>440	2 (0.2)	1 (0.4)	-	2 (0.1)	1 (0.3)	3 (0.1)	7 (0.3)
Total Bilirubin (umol/L)								
normal	0-17	1155 (99)	279 (98)	724 (94)	1438 (91)	264 (92)	2426 (92)	2250 (88)
>ULN to 3 x ULN	18-51	9 (0.8)	2 (0.7)	46 (6)	141 (9)	23 (8)	210 (8)	308 (12)
>3 x ULN to 5 x ULN	52-85	1 (0.1)	-	-	1 (0.1)	-	1 (0.03)	-
>5 x ULN to 8 x ULN	86-136	-	-	-	-	-	-	-
>8 x ULN	>136	-	-	1 (0.1)	-	-	1 (0.03)	-

*Includes MTX

Escape data are excluded

Sources: Tables stlb_shift_blow_bchem of Module 2.7.4 Summary of Clinical Safety and 120 day safety update

Patients treated with tocilizumab experienced elevations in LDL levels. This finding is of concern given the known association between elevated LDL levels and cardiovascular risk. During the clinical trials elevations in LDL were treated according to the judgment of the treating physician with lipid-lowering agents as indicated. As shown in Table 9, elevations to markedly abnormal values were uncommon (2% of patients). The occurrence of new starts of statins were similar between tocilizumab-treated patients and controls. Examination of the rate of atherosclerotic cardiovascular events showed that they were similar in the controlled portions of the clinical, that those event rates did not increase with longer durations of exposure and that the rate of stroke and myocardial infarction (MI) was in the same range or lower than that seen in epidemiologic studies of RA patients.

Table 9: Markedly Abnormal Lipid Parameters

Markedly Abnormal Lipid Parameters in the Tocilizumab RA Pivotal Studies and Long-Term Extensions									
			6-months pooled safety population						Long term safety population
	normal range	markedly abnl def.	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	2562
Pts discontinued for abnl			-	-	-	-	-	-	1 (<1)
Dose mod/interrupted			-	-	-	-	-	-	5 (<1)
Lipid lowering agent started			13 (1)	2 (1)	15 (2)	19 (1)	3 (1)	37 (1)	180 (7)
Cholesterol (mmol/L)	(0-6.18)	>8.30							
single, not last value			1 (<1)	2 (<1)	14 (2)	30 (2)	11 (4)	55 (2)	103 (4)
last value or replicated			1 (<1)	0	6 (<1)	28 (2)	12 (4)	46 (2)	82 (3)
any value			2 (<1)	2 (<1)	20 (3)	58 (4)	23 (8)	101 (4)	185 (7)
HDL (mmol/L)	(0.91-n.d.)	<0.65							
single, not last value			0	0	0	1 (<1)	2 (<1)	3 (<1)	10 (<1)
last value or replicated			1 (<1)	1 (<1)	2 (<1)	1 (<1)	0	3 (<1)	5 (<1)
any value			1 (<1)	1 (<1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	15 (<1)
LDL (mmol/L)	(0-4.13)	>5.4							
single, not last value			3 (<1)	3 (1)	17 (2)	37 (2)	12 (4)	66 (3)	128 (5)
last value or replicated			3 (<1)	1 (<1)	13 (2)	58 (4)	17 (6)	88 (3)	144 (6)
any value			6 (<1)	4 (1)	30 (4)	95 (6)	29 (11)	154 (6)	272 (11)
Triglycerides (mmol/L)	(0.45-1.89)	>2.83							
single, not last value			7 (<1)	1 (<1)	38 (5)	77 (5)	20 (7)	135 (5)	245 (10)
last value or replicated			9 (<1)	0	23 (3)	77 (5)	19 (7)	119 (5)	185 (7)
any value			16 (1)	1 (<1)	61 (8)	154 (10)	39 (14)	254 (10)	430 (17)

*Includes MTX
Worst values within a time window per patient are summarized
Escape data is excluded
Sources: Table stlb10_mark of Module 2.7.4, Pg. 94 and Tables stae11_wd, stae11_dmod, stlb10_ldl_ssta and stlb10_mark of 120 day safety update

Although no clinical cardiovascular safety signal was observed in the tocilizumab studies it is nonetheless important to carefully consider the potential for risk over time in view of the increase in LDL in some patients. Cardiovascular risk is of particular concern since RA patients are known to be at increased risk of MI and stroke. However, it should also be considered that exploration of the causes of increased risk of cardiovascular events in RA has not clearly tied this increased risk to traditional risk factors such as elevated lipid levels. An important potential contributor is the chronic inflammation in patients with RA. Chronic inflammation has been tied to cardiovascular risk in several ways, including elevation of CRP levels, a known risk factor for cardiovascular disease, and evidence that RA patients may have some features of the metabolic syndrome. To the extent that tocilizumab decreases inflammation it may have salutary effects on cardiovascular risk. Clearly cardiovascular risks should be studied further in patients receiving tocilizumab. Consults have been submitted to the Cardiorenal division and the Endocrine division for their assessment of the risks of LDL elevation in patients receiving tocilizumab and what studies would be most appropriate to evaluate further.

A total of four patients in the safety database were observed to experience demyelinating neurologic events. The underlying rate of these events in the RA population is not known. Demyelinating events have been observed among patients receiving other immunosuppressive biologics for RA, in particular TNF blockers.

6.3.3. Safety update

The results of the safety update are included in the discussion above.

6.3.4. Immunogenicity

Immunogenicity was infrequent in the tocilizumab clinical development program (under 2% of patients). Antibodies to tocilizumab were not more frequent with tocilizumab monotherapy. Antibodies to tocilizumab were not significantly associated with either a particular pattern of adverse events or with loss of efficacy.

6.3.5. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer concluded that the safety profile of tocilizumab was commensurate with that of other immunosuppressants used as disease-modifying agents in RA. Dr. Okada identified serious infections, the effects on laboratory parameters and the uncommon serious adverse events GI perforation and demyelination to be the most important safety events to consider in determining the overall risk/benefit profile for tocilizumab. Dr. Okada recommends continued study of long-term open-label treatment and a large registry to more fully capture safety issues that may arise with long-term tocilizumab treatment.

6.3.6. Discussion of notable safety issues

Overall, the major safety issues with this application are serious infections, GI perforations, laboratory abnormalities (liver enzyme elevations, decreases in hematologic parameters and increases in LDL levels) and demyelinating events. The serious infections are commensurate with what has been seen with approved immunosuppressive treatments for RA. The GI perforations and demyelinating events are very uncommon events. Product labeling should clearly alert patients and prescribers to the possibility of their occurrence and more data should be collected on the level of risk in postmarketing studies. Laboratory abnormalities in liver enzymes and hematologic parameters were observed and these laboratories should be closely monitored if tocilizumab is approved. The major unresolved issue concerns increases in LDL levels. Currently, consults are pending with the Cardiorenal division and the Endocrine division about the degree of cardiovascular risk and how this risk may be studied further. Counterbalancing the possibility of increased risk associated with tocilizumab use is the fact that cardiovascular events rates in the tocilizumab database compared favorably to event rates reported in the literature and that the anti-inflammatory properties of tocilizumab may have a salutary effect on cardiovascular risk in RA.

7. Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee was held on July 29, 2008 to discuss the tocilizumab application. The members of the committee concurred that efficacy was demonstrated in RA. They were uncertain whether the data clearly indicated a benefit of 8 mg/kg over the 4 mg/kg dose in patients with an inadequate response to DMARD's. They judged that the risk of serious infection was similar to that seen with commonly used agents in RA. They discussed the uncommon adverse events of GI perforation and demyelination but did not believe that their occurrence outweighed the benefits observed with the product. The main area under discussion was the potential risk conferred by the

elevation in LDL levels. Some members expressed great concern while other members were reassured by the lack of a signal for clinical cardiovascular events and by the potentially beneficial anti-inflammatory effects of tocilizumab on cardiovascular risk. The committee voted 10-to-1 in favor of approval.

8. Financial Disclosure

No potentially conflicting financial interests were identified.

9. Labeling

9.1. Proprietary name

DMETS determined that the proposed proprietary name, Actemra, was acceptable.

9.2. Physician labeling

At the time of completion of this CDTL memo, detailed consideration of the label were just beginning. The label should include explicit recommendations for monitoring for laboratory abnormalities. In addition, based on consideration of the possible effect of tocilizumab on P450 levels the possibility of drug-drug interactions should be incorporated in physician labeling, per recommendations of Clinical Pharmacology.

10. DSI audits

DSI inspected 5 sites – 2 in the US and 3 in Mexico. DSI concluded that the studies were conducted adequately and may be used to support the BLA.

11. Conclusions and recommendations

11.1. Regulatory action

Data from five adequate and controlled trials of tocilizumab demonstrated clinically meaningful and statistically significant efficacy in patients with moderately to severely active RA. In patients with an incomplete response to MTX or other DMARD's ACR 20 response rates of 56-61% were observed, compared to placebo control responses of approximately 25%. Efficacy was also demonstrated in patients who had previously shown an incomplete response to prior TNF blocker treatment. In a head-to-head trial comparing tocilizumab to MTX in MTX-naïve patients responses to tocilizumab were demonstrated to be non-inferior to MTX and in a subsequent analysis a higher rate of response was demonstrated. Clinical benefit was observed across all the components of the ACR response criteria, including patient-reported measures, physician measures and laboratory measures. Clinical responses were maintained out to 6 months with continued treatment.

Treatment with tocilizumab is associated with several safety issues. Serious infections are seen more frequently with tocilizumab treatment. There is the uncommon occurrence

of GI perforations and demyelinating events. Tocilizumab impacts several laboratory parameters, including liver enzymes, lipid levels and hematologic parameters. If tocilizumab is approved these safety concerns should be described in the label and patients should be carefully monitored for these laboratory abnormalities. In general, this safety profile is similar to what has been observed with other disease-modifying agents used in patients with RA.

The one unresolved issue is the impact of the lipid abnormalities. Patients receiving tocilizumab have increases in LDL levels, a known risk factor for cardiovascular adverse events. Marked elevations were uncommon and the need to start lipid-lowering therapy was not more common in patients receiving tocilizumab than in controls. Cardiovascular event rates were not elevated in controlled trials and compared favorably to event rates reported in the literature. Counterbalancing the concern about increased cardiovascular event rates with tocilizumab is the possibility of decreased cardiovascular risk due to the anti-inflammatory properties of the product.

Several issues must be resolved before this BLA can be approved. The issues regarding deficiencies at the manufacturing plant must be addressed satisfactorily and a determination must be made about the degree of cardiovascular risk the elevation in LDL levels may impart. Currently, consults are pending with the Cardiorenal division and the Endocrine division for their assessment of the potential risk and their recommendations for how that potential risk may be assessed further.

If the issues regarding CMC and the potential cardiovascular risk can be resolved this BLA should be approved with appropriate modifications to the proposed package insert.

11.2. Safety concerns to be followed postmarketing

The major safety concerns that should be followed postmarketing are serious infections, GI perforations, cardiovascular risk, clinical hepatotoxic events, events relating to abnormalities in hematologic parameters and demyelinating events.

11.3. Risk Evaluation and Mitigation Strategy (REMS)

11.3.1. General considerations on the need for, and goals of, any REMS beyond standard labeling and pharmacovigilance

A REMS should be required for tocilizumab for several reasons. First, because of the toxicities associated with tocilizumab patients a Medication Guide should be required to inform patients about their occurrence and to alert them to bring themselves to medical attention if they experience symptoms suggestive of a GI perforation or serious infection. In addition, a REMS should be required because of the need for monitoring of liver enzymes, hematologic parameters and lipids. The REMS should contain provisions for educating prescribers about the need for careful monitoring and assess whether prescribers are following recommendations for monitoring.

11.4. Postmarketing studies

11.4.1. Required studies

If tocilizumab is approved there should be several studies required. The applicant should continue the ongoing long-term, open-label treatment studies out to 5 years to further assess long-term safety of tocilizumab. They should additionally conduct a registry to include an internal control arm to assess the relative rates of important adverse events including cardiovascular events, malignancies, GI perforation events, clinical hepatotoxic events that may be associated with use of tocilizumab. They should conduct a controlled trial of the effects of tocilizumab on therapeutic vaccination. Finally, to fulfill PREA requirements, they should conduct a study in children with polyarticular JIA.

11.4.2. Commitments (PMCs)

No additional PMC's are necessary.

11.4.3. Other agreements with Sponsor

None.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	September 7, 2008
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125276
Applicant Name	Hoffmann-LaRoche
Date of Submission	November 19, 2007
PDUFA Goal Date	September 18, 2008
Proprietary Name / Established (USAN) Name	Actemra Tocilizumab
Dosage Forms / Strength	Injectable, 20 mg/mL aqueous solution for intravenous injection
Proposed Indication	For the treatment of adult patients with moderate to severe active rheumatoid arthritis alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs
Recommendation for action:	Complete Response
Signature and date:	9/10/08

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Sarah Okada, M.D.
Statistical Review	Joan Buenconsejo, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Asoke Mukherjee, Ph.D.; R. Daniel Mellon, Ph.D.
OBP Quality Review	Gerald M. Feldman, Ph.D.; Marjorie A. Shapiro, Ph.D.; Kathleen A. Clouse, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Lei Zhang, Ph.D.; Suresh Doddapaneni, Ph.D.; Venkatesh Atul Bhattaram, Ph.D.; Jogarao Gobburu, Ph.D.
Division of Cardiorenal Products	Shari L. Targum, M.D.; Norman Stockbridge, M.D., Ph.D.
Division of Metabolic and Endocrine Products	Eileen Craig, M.D.; Eric Colman, M.D.
DDMAC	Michelle Safarik, PA-C
DSI	Susan Leibenhaut, M.D.
CDTL Review	Jeffrey Siegel, M.D.
OSE IO	John R. Senior, M.D.
OSE/DMEPA	Tara Turner, Pharm.D.; Linda Kim-Jung, Pharm.D.; Denise Toyer, Pharm.D.
OSE/DAEA	N/A
OSE/DRISK	N/A
OSE/DEPI	N/A

OBP=Office of Biotechnology Products
OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology

1. Introduction

Actemra is an aqueous solution for intravenous injection of tocilizumab, a monoclonal antibody that binds to the interleukin-6 (IL-6) receptor, inhibiting the biological activity of IL-6 and thereby reducing the production of acute phase reactants that are thought to play a role in the underlying inflammatory pathophysiology of rheumatoid arthritis. This is a "first in class" product submitted by Hoffmann-La Roche for licensure as BLA 125276. IL-6 also acts as a growth factor for certain cells and regulates cells of the immune system.

Actemra was approved in Japan in April 2005 for the treatment of multicentric Castleman's disease. [ ] In April 2008, tocilizumab was approved in Japan for the treatment of adult RA, systemic juvenile idiopathic arthritis (SJIA) and polyarticular juvenile idiopathic arthritis (PJIA). b(4)

2. Background

The sponsor has submitted data from an extensive Phase 3 development program. While the efficacy of Actemra appears to have been clearly established, a number of safety signals arose during review of the application. These safety signals include serious infections, gastrointestinal perforations, central and peripheral demyelinating disorders, and laboratory evidence of hepatoxicity, elevated lipids and decreases in neutrophil and platelet counts. Based on the fact that this is a first in class product, and because of the safety concerns documented during the review, this application was presented to the members of the Arthritis Advisory Committee at an open public meeting on July 29, 2008.

3. CMC

The recommended expiration dating period for Actemra vials is 24 months from date of manufacture when stored under refrigeration at 2° C to 8° C and in the original carton in order to protect it from light.

Dr. Shapiro states the following on page 6 of her summary:

> Tocilizumab is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Tocilizumab is manufactured consistently, leads to a safe and effective product, and approval is recommended for the proposed indication.

However, as per Dr. Siegel's review, there were major deficiencies at the manufacturing facility in Japan, including infestation, failure of sterile processes and the use of _____ in one testing procedure. The sponsor reports that these deficiencies have been rectified, but that information was recently received and remains under review at this time. b(4)

4. Nonclinical Pharmacology/Toxicology

The only outstanding concerns raised by the primary pharmacology/toxicology review, Dr. Mukherjee, are the absence of carcinogenicity and Segment 3 reproductive toxicology studies. It should be noted that Dr. Siegel's statement on page 6 of his review, attributed to Dr. Mellon, that, "...the Agency had previously agreed that carcinogenicity studies and seg 3 studies would not be needed for approval of tocilizumab." is not entirely correct. While the sponsor was informed that carcinogenicity studies would not be required for approval, the Division has consistently stated in meetings for which there is clear documentation that Segment 1 and Segment 3 studies would be required for approval.

Dr. Mellon has provided a supervisory review in which he concludes that (from page 2 of that review):

> Dr. Mukherjee has recommended that the BLA not be approved at this time due to the lack of any non-clinical data on the carcinogenic risks following treatment with an IL-6R antibody. Dr. Mukherjee specifically recommended that the Applicant use their species-specific monoclonal antibody to IL-6R (homologous product) to conduct fertility, segment 3 reproductive toxicity and carcinogenicity studies. He does not consider the lack of reproductive and developmental toxicity data necessary for approval, as there are potentially some patients who may benefit from the product who are not of child-bearing potential.
>
> From a nonclinical pharmacology toxicology perspective, I concur that there are inadequate data to support approval of this product at this time. However, it is my opinion that the lack of adequate reproductive and developmental toxicity data should be considered an approval issue, since limiting distribution to only individuals who are not of child-bearing potential is not feasible.
>
> Although traditional carcinogenicity studies would be ideal for any drug product, the ability to conduct such studies for this product is likely very limited, and the potential for this product to increase the risk of malignancy can not be clearly eliminated. As such, this concern can be addressed in the product labeling.

On pages 2 and 3 of his review, Dr. Mellon recommends the following studies be performed prior to approval:

1. Although requested at the time of the preBLA meeting, the Applicant has not conducted peri-natal and post-natal developmental toxicology studies nor have they provided adequate justification for why such studies are not possible. Consistent with the recommendations made at that time, the Applicant should conduct a peri-natal and post-natal developmental toxicology study using either the monkey or the surrogate model prior to approval of this product.

2. Although adequate fertility studies are not feasible in the primate model, the Applicant appears to have a mouse homologous product that can be used to characterize the potential effects on fertility. As the Applicant has not provided adequate justification for why fertility studies in the surrogate model are not possible, such studies should also be completed prior to approval of this product.

In addition, Dr. Mellon also recommends the following studies that are not necessary for approval:

3. Although not an approval issue, the Applicant has stated that the homologous protein is not a viable option for carcinogenicity assessment. Specifically, they state that "The MR16-1 antibody is also not an appropriate reagent to be used in long term carcinogenicity studies, as this antibody is a rat monoclonal anti-mouse IL-6R antibody and is considered to be immunogenic in long term in vivo studies in mice." As Dr. Mukherjee's review notes, there are no data to support this conclusion in the BLA. The Sponsor should be asked to provide data to support this statement in order to support their conclusion that this option for carcinogenicity assessment is not possible. Upon review of these data, this issue may need to be reassessed.

4. Although not an approval issue, the Applicant should submit a summary table comparing the binding affinity of tocilizumab to both the human and monkey sIL-6R and mIL-6R and a comparison of the functional potency of tocilizumab at the human and monkey IL-6R with references to the studies from which the data were obtained. Although not critical for approval due to the existing human experience, these data are necessary to assist in the extrapolation of the findings in the toxicology program to humans, as described in ICHS6.

5. Clinical Pharmacology/Biopharmaceutics

The following is reproduced from Dr. Siegel's summary of the clinical pharmacology of Actemra on page 6 of his review:

> 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 T1/2 was 201 hours (8 days). PK was similar in patients with RA.
>
> A population PK analysis demonstrated a non-linear component of clearance at low concentrations of tocilizumab and a linear component at higher concentrations. The non-linear component is more important at the 4 mg/kg dose than at the 8 mg/kg dose. Linear clearance increased with increasing body weight.

Although population pharmacokinetic data did not demonstrate any apparent drug-drug interactions with commonly administered agents used to treat RA, IL-6 is known to decrease P450 activity. As such, inhibition of IL-6 by Actemra could increase CYP 450 activity. In one in vivo study, co-administration of tocilizumab 8 mg/kg resulted in a 50% decrease in exposure of omeprazole in CYP 2C19 extensive metabolizers. Based on this, Dr. Zhang recommends labeling language specifically informing prescribers of the potential for interactions possibly leading to changes in the serum levels of drugs that are P450 substrates with a narrow therapeutic index.

I concur with the OCP review team that there are no outstanding concerns regarding the clinical pharmacology and biopharmaceutics of Actemra.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The sponsor chose a dose of 8 mg/kg every 4 weeks based on a dose-finding study completed by Chugai Pharmaceuticals in Japan. This was a randomized, 20-week trial in RA patients that compared 2, 4 and 8 mg/kg of Actemra to placebo administered every 4 weeks. The results of this study demonstrated higher ACR 20 responses for the 4-mg/kg and 8-mg/kg doses than the 2-mg/kg dose. However, higher level responses, the ACR 50 and 70 responses, occurred more frequently with the 8-mg/kg dose.

On page 8 of his review, Dr. Siegel summarizes some of the discussion related to this choice of dose by members of the AAC:

> At the July 29, 2008 meeting of the Arthritis Advisory Committee Hoffman-La Roche showed a slide of the individual components of the ACR response criteria in a trial comparing 4 mg/kg to 8

mg/kg to placebo. Dr. David Felson, a panel member, pointed out that most of the individual components showed little difference between 4 mg/kg and 8 mg/kg and that the component driving the differences between 4 and 8 mg/kg was primarily the laboratory component, the CRP, which showed large differences between 4 and 8 mg/kg. He argued that therefore the correct initial dose for DMARD incomplete responders was 4 mg/kg. He acknowledged that in other patient groups, e.g., TNF blocker incomplete responders, that 8 mg/kg provided better efficacy than 4 mg/kg. Other members of the panel agreed with Dr. Felson.

Dr. Siegel states that, although the 4- and 8-mg/kg doses have similar effects on the "symptom" components of the ACR response, the 8-mg/kg dose achieves somewhat better improvement in each of the components of the ACR response. He notes that the component with the largest difference in effect is the acute phase reactants component, a measure of inflammation. He adds that patients with an inadequate response to a TNF blocker also showed greater responses on the ACR 20 with the 8-mg/kg dose compared to the 4-mg/kg dose, while only the 8-mg/kg dose was studied in the setting of monotherapy so that any differential due to dose is unknown for that sub-population. He states that the safety of the 4-mg/kg and 8-mg/kg doses is generally similar. Finally, he notes that as, even in the face of elevated LDL levels, there was no signal of cardiotoxicity in the clinical studies, the increased risk associated with the lipid elevations may be counterbalanced by a reduction in risk due to decreased CRP levels. While this hypothesis is interesting, it remains speculative. I would disagree with Dr. Siegel's characterization of the safety profile of the two doses, if for no other reason than, at this time, there is an apparent dose-related risk of gastrointestinal perforation which only occurred in the 8-mg/kg dose arm.

The sponsor submitted data from five Phase 3 trials of Actemra in RA patients. Two, WA17822 and WA17833, studied Actemra compared to placebo in patients on a stable dose of methotrexate (MTX). Study WA18062 evaluated Actemra compared to placebo in RA patients who had previously had an inadequate response to TNF blockers. Study WA18063 studied Actemra or placebo added to any non-biologic DMARD therapy that the enrolled RA patients were previously receiving. The fifth study, WA17824, was a non-inferiority trial comparing Actemra to MTX and placebo in patients who were not receiving any DMARDs at the time of enrollment.

The following table summarizes the results of the five trials and has been reproduced from page 12 of Dr. Siegel's review:

Table 1: Proportion of ACR20/50/70 Responders at Week 24

Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment (ITT Populations)						
Study	Pbo + DMARD**	TCZ 4mg/kg + DMARD**	TCZ 8mg/kg + DMARD**	p-value (4 mg/kg)	p-value (8 mg/kg)	
Patients with incomplete response to MTX or other DMARDs						
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	
WA18063	(n=413)		(n=803)			
ACR20	24		61		<0.0001	
ACR50	9		38		<0.0001	
ACR70	3		20		<0.0001	
Patients with incomplete response to prior TNF inhibitor treatment						
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	
MTX naïve/Early RA patients						
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 for primary analysis population

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 19 of WA17822 CSR, Tables 17 & 18 of WA17823 CSR, Tables 17 & 22 of WA17824 CSR
Tables 21 & 23 of WA18062 CSR, and Tables 17 & 20 of WA18063 CSR

8. Safety

The safety database for Actemra includes the results of the clinical studies performed specifically for this application, in addition to data collected in Japan from clinical studies in multicentric Castleman's disease and JIA, and postmarketing data in Castleman's disease patients. Overall, 3778 RA patients have been exposed to Actemra in clinical studies, with 3474 exposed for at least 6 months, 2121 for at least one year and 640 for 2 years or longer. Most of these patients were treated with the 8-mg/kg dose, although over a thousand patients were treated with the 4-mg/kg dose.

Twenty-one Actemra-treated subjects died in the RA clinical studies. While 4 placebo-treated subjects died during the studies, as the placebo-treated subjects were allowed early escape, a comparison between the two groups must take into consideration overall exposure by time. On page 52 of her review, Dr. Okada states that, "Overall, the exposure-adjusted incidence rates of death were not elevated in the TCZ treatment groups compared to the placebo or MTX monotherapy treatment groups, with the exception of the TCZ 8 mg/kg monotherapy treatment

group (1% or 2.4/100 pt-yrs compared to 0.3% or 0.9/100 pt-years with placebo). This finding is difficult to interpret because of the small number of deaths involved, namely 3 among 288 patients receiving TCZ 8 mg/kg monotherapy." She also notes that the Actemra 8-mg/kg combination with DMARDs arm does not show a higher rate of death than the placebo or MTX-monotherapy arms, therefore making the finding in the Actemra 8-mg/kg monotherapy arm questionable. Perhaps most importantly, the overall number of deaths in Actemra exposed subjects appeared to be consistent with that seen in the underlying RA patient population.

The major serious adverse events of concern were malignancies, serious infections, cerebrovascular events, gastrointestinal perforations, peripheral and central demyelinating events, and laboratory abnormalities, specifically hematologic abnormalities, elevated lipids, and hepatic enzyme and bilirubin elevations. The rates for malignancies, serious infections and cerebrovascular events were not elevated above the exposure-adjusted rates for RA patients found in the literature. Exposure-adjusted rates for malignancy in the Actemra subjects were also not elevated in comparison to the rates in the placebo or MTX subjects.

Serious infections did occur more frequently in the Actemra 8-mg/kg subjects compared to the placebo subjects. These rates became equivalent with longer duration of exposure. Serious infections occurred at a higher rate in the 8-mg/kg arm compared to the 4-mg/kg arm. Dr. Siegel states that the types of serious infections seen were similar to those seen with other immunosuppressive DMARDs. Two cases of opportunistic infections occurred in Actemra-treated patients, one case of pneumocystis jiroveci pneumonia and one case of mycobacterium avium intracellulare pneumonia.

Gastrointestinal perforations occurred in three Actemra 8-mg/kg treated subjects in 6-month controlled period of the Hoffman-LaRoche RA studies. None of these events occurred in the other treatment arms. There were eleven total events of gastrointestinal perforation in the Hoffmann-LaRoche studies, including the long-term extension studies. While it is true that concomitant use of NSAIDs and/or corticosteroids may have played a role in these events, these background medications were also used in many of the patients in the placebo, MTX and 4-mg/kg Actemra treatment groups. In the global RA programs including subjects from both the Hoffman-LaRoche and Chugai development programs sixteen gastrointestinal perforations occurred, almost all at the 8-mg/kg dose. Table 26, reproduced below from page 66 of Dr. Okada's review, summarizes the exposure-adjusted incidences of these events and compares those rates to rates found in two available databases for RA patients.

Table 2 Exposure Adjusted Incidence of GI Perforations

Exposure-Adjusted Incidence of GI Perforations in RA Patients				
	TCZ program Events	TCZ program Events/100 pt-yrs	UHC database Events/100 pt-yrs	Marketscan database Events/100 pt-yrs
Upper GI	4	0.05	0.03	0.02
Lower GI	12	0.15	0.16	0.14
Total	16	0.20	0.18	0.16

Data cut-off December 31, 2007

Sources: Tables 14 and 15 of 120 day safety update

Four patients in the global Actemra program developed demyelinating disorders. Three of these events were central, two of which may well have been cases of multiple sclerosis or a multiple sclerosis-like syndrome. The fourth event was peripheral and was diagnosed as chronic idiopathic polyradiculoneuropathy. Three of these cases occurred on Actemra 8 mg/kg and the fourth case remains blinded at this time. It is difficult to assess the significance of these events, but MS does occur at a fairly high frequency, with a worldwide incidence of approximately 0.1%. Demyelinating events have also been observed in RA patients treated with other immunosuppressive biologic products such as the TNF blockers.

There was a concerning finding of an increased incidence of elevated liver enzymes in the Actemra-treated subjects. Although there were no clinical events of hepatitis or hepatic failure reported in the studies, these laboratory abnormalities do suggest a signal for possible hepatoxicity. Elevated enzymes occurred most frequently in the Actemra 8-mg/kg plus DMARD-treated subjects. Most of the elevations responded to a reduction in Actrema dose, a reduction in the DMARD dose, and/or a temporary interruption in Actemra treatment. On page 76 of her review, Dr. Okada notes the following:

> Although the mechanism of action of liver enzyme abnormalities with tocilizumab has not been ascertained, there are plausible mechanisms by which hepatocellular injury could occur with anti-IL6R treatment. First, IL6 appears to have a hepatoprotective effect on various forms of liver injury and promotes hepatocyte regeneration. Therefore inhibition could lead to increased hepatocyte susceptibility to hepatotoxic insults.
> Also, hepatocytes express high levels of IL6 receptor; which raises the question of whether, with ubiquitous anti-IL6R monoclonal antibody binding in the liver, even minimal complement-mediated cytotoxicity or antibody-dependent cellular cytotoxicity could result in some hepatic injury.

A single case of enzyme and bilirubin elevations in a patient treated with 8 mg/kg of Actrema alone for the first six months and then with MTX 20 mg during the long-term extension period, that was initially thought to be a Hy's Law case by the review team, was fully evaluated by Dr. John Senior, a hepatology expert in the Office of Surveillance and Epidemiology. Dr. Senior determined that this case did not fit the criteria for Hy's Law as the patient had evidence of underlying Gilbert syndrome. Nevertheless, Dr. Senior did conclude that this patient clearly experienced drug induced liver injury based on the extremely high enzyme elevations and on the fact that the enzyme and bilirubin levels decreased with discontinuation of the drug and then increased again on rechallenge with half-doses of Actemra and MTX. He does note, however, that other possible causes (acute viral hepatitis, autoimmune hepatitis, biliary tract disease, etc.) have not been adequately excluded. Dr. Senior also notes that the sponsor has inadequately assessed and evaluated the findings of abnormal liver function in general, and in this case in particular. The clinical review team has concluded that monitoring of liver enzymes should be recommended in the product label, along with recommendations for dose modification in the face of an abnormal finding. Among his recommendations in his second consult, Dr. Senior states that, "I do not think this case justifies a recommendation for monitoring, but some mention of it should be included in the labeling, with suggestion that future cases should be looked for, especially in patients taking combinations of drugs with tolizumab (sic), and that cases that occur be investigated thoroughly and reported completely."

Subjects in the Actemra-treatment groups demonstrated a greater incidence of decreases in their WBC counts and neutrophil counts, but these laboratory findings were not associated with adverse events of infection. Subjects in the Actemra-treatment groups also demonstrated a greater incidence of decreased platelet counts, but these counts remained within the normal range and were not associated with adverse events of abnormal bleeding. The clinical review team has concluded that monitoring for these hematologic parameters should be recommended in the product label. Subjects in the Actemra-treatment groups also demonstrated a concerning signal for significant elevations in total cholesterol, LDL and triglycerides. The review team has concluded that, in the absence of a signal of increased cardiovascular events, it is sufficient that monitoring for these elevations should be recommended in the product label. Consults regarding the elevated lipids have been sent to the Division of Cardiorenal Products and the Division of Metabolic and Endocrine Products. The DEMP reviewers have concluded that the cardiovascular risk related to the apparent lipid profile changes associated with exposure to Actemra is unclear based on the limited patient exposure over time in this database. They recommend either requiring a cardiovascular outcome study or, if that is impractical, providing adequate language in the label to caution prescribers and patients and to assure adequate monitoring of lipid levels. The reviewers from the Division of Cardiorenal Products concurred that there was no adverse cardiac signal observed in the study database. However, as the event rates were low in all treatment groups, they were unable to draw definitive conclusions regarding cardiovascular risk. They note that the highest risk patients were not studied and that the duration of treatment was not long enough to allow for the occurrence of an adequate number of events. In addition, they they comment that, "...at the present time one cannot predict net cardiovascular risk on the basis of drug-associated lipid increases due to multiple and complex effects of drugs." (Dr. Targum's review, page 4)

9. Advisory Committee Meeting

As noted above, although the AAC members concluded that efficacy had been clearly established for Actemra based on the clinical trials, they remained uncertain as to whether the data demonstrated a clear benefit of the 8-mg/kg dosing regimen over the 4-mg/kg dosing regimen in patients with an inadequate response to DMARDs. They concurred with the review team's analyses of the major safety concerns with one exception. As per the quotation above from Dr. Siegel's review, Dr. Felson and others expressed some concern regarding the lipid abnormalities and the possible impact of this finding on the cardiovascular safety of Actemra in the already high risk RA population. However, they made no specific recommendations other than the need for monitoring. The committee members voted 10 to 1 for approval of this product. The consumer advocate, Ms. Diane Aronson, voted against approval expressing concern about the safety findings in the absence of a major advantage over the approved products for the treatment of RA.

10. Pediatrics

From page 13 of Dr. Siegel's review:

The applicant has requested a deferral for patients age 2-17 with polyarticular juvenile idiopathic arthritis (JIA), and a waiver for children 0-2. The applicant has already discussed details of their proposed Phase 3 program in polyarticular JIA with the Agency. This study is planned to commence enrollment in the 4th quarter of 2008, with submission of the final study report planned for 2012. The applicant's proposed plan for studies in children appears adequate.

11. Other Relevant Regulatory Issues

Both Drs. Okada and Siegel have recommended that a REMS should be required for Actrema approval. Their recommendation is based on the need for a MedGuide to alert patients to early signs of infection and gastrointestinal perforation, as well as the need for monitoring of hepatic, lipid and hematologic parameters.

12. Labeling

The review team proposed a number of labeling changes to the package insert as discussed above and these changes have been recently forwarded to the sponsor.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action

  Complete Response

- Risk Benefit Assessment

  While the sponsor has clearly demonstrated that Actemra is effective as a treatment for RA, I do not think that they have adequately assessed the risk-benefit ratio for their choice of recommending the 8-mg/kg dose. Overall, this dose does not appear to provide a significant benefit for most patients compared to the 4-mg/kg dose. While there may be some subpopulations or individual doses that would achieve greater benefit from the higher dose, there also appear to be possible safety concerns that are dose related, in particular the risk of gastrointestinal perforation. In addition, the increased efficacy associated with the higher dose appears to be primarily driven by the product's effect on the CRP levels. The actual clinical components of the ACR20 demonstrate less of an advantage for the higher dose. The sponsor should further evaluate the risk, as well as the overall risk-benefit, of recommending only the 8-mg/kg dose, or consider recommending starting with the lower dose and increasing to the higher dose as needed and as tolerated.

  While the overall risk-benefit profile for Actemra appears reasonable, there are safety concerns that will need to be adequately addressed before this product should be approved. While I think that the risks of serious infection and gastrointestinal perforation can be partially addressed in the package insert, I

agree with the clinical review team that a MedGuide is necessary to provide patients with adequate warning of early signs and symptoms of these conditions. Requiring a MedGuide necessitates a requirement for a REMS. In addition, a REMS will be necessary to ensure laboratory monitoring for abnormal hepatic, hematologic and lipid parameters. (See discussion below.) Of note, while the hepatic enzyme and bilirubin abnormalities appeared to be more common in subjects treated with Actemra and MTX, this is likely to be the more commonly prescribed treatment regimen compared to Actemra monotherapy.

This application should not be approved until the sponsor has submitted the results of preclinical studies that provide adequate reproductive and developmental toxicity data to assure safe use and provide informed language in the label. Finally, assurance that the manufacturing facility has adequately addressed all of the deficiencies noted at inspection will be necessary prior to approval.

During a recent discussion with Dr. Curtis Rosebraugh, Director, Office of Drug Evaluation II and signatory authority for this application, he noted that, based on the numerous safety concerns that have surfaced during our review of this application and the availability of a number of other effective products for the treatment of RA, he would likely require that, when the application is approved, it only be indicated for patients who have had an inadequate response to other available DMARDs including TNF blockers. I agree that this would be an effective means of assuring safe use while further data is captured in the postmarketing setting, but still maintain availability for patients who do need this product. The indication could then be broadened once the sponsor has provided adequate data to support wider use.

- Recommendation for Postmarketing Risk Management Activities

A REMS should be required for this product's approval in order to address the need for a MedGuide and adequate laboratory monitoring not only to assure patient safety but also to provide data to assess the actual risks associated with Actemra. Though Dr. Senior states that he does not think monitoring of hepatic enzymes and bilirubin is necessary, he also states that, "... some mention of it [monitoring] should be included in the labeling, with suggestion that future cases should be looked for, especially in patients taking combinations of drugs with tolizumab (sic), and that cases that occur be investigated thoroughly and reported completely." Recommending monitoring in product labels is known to result in a rather low rate of compliance. It seems essential to me that, at least during the first few years after product launch, health care practitioners monitor their patients treated with Actemra in order to assure their safety, as well as to capture the data that will be necessary to determine whether these early laboratory signals are of real clinical significance. This would also apply to the hematologic and lipid signals found in the clinical studies database. A REMS

would place the responsibility to assure routine laboratory monitoring in the hands of the sponsor, which is entirely appropriate. The absence of a clear increase in cases of clinical hepatic, hematologic or cardiovascular abnormalities in the clinical studies database does not ensure that these events will not occur once the product is more widely prescribed in the community. Even a rare case of hepatic failure is not tolerable if it could have been prevented. This applies to the severe morbidity and even death that could result from significant reductions in the WBC, neutrophil or platelet counts. Finally, long-term cardiovascular damage due to abnormal lipid parameters could easily go undetected for years, if not decades.

In addition, the REMS should include requirements for the sponsor to undertake the following studies:

1) Continuation of their ongoing, long-term, open-label studies out to five years to further assess the long-term safety of Actemra.
2) A registry that includes an internal control arm to assess the relative rates of important adverse events including cardiovascular events, malignancies, gastrointestinal perforations and hepatic events such as hepatitis and hepatic failure.
3) A controlled trial of the effects of Actemra on therapeutic vaccination.
4) A registry that includes an internal control arm that will assess the effects of Actemra on pregnant women and children exposed during pregnancy.
5) A study in children with polyarticular JIA to fulfill their requirements under PREA.

- Recommendation for other Postmarketing Study Commitments

Based on the sponsor's contention that their homologous protein is not a viable option for carcinogenicity assessment and the fact that Drs. Mukherjee and Mellon have determined that there are no data to support that conclusion in the BLA, the sponsor should be asked to provide data to support their conclusion that this option for carcinogenicity assessment is not possible.

As per Dr. Mellon's recommendation, the sponsor should submit a summary table comparing the binding affinity of tocilizumab to both the human and monkey sIL-6R and mIL-6R and a comparison of the functional potency of tocilizumab at the human and monkey IL-6R with references to the studies from which the data were obtained. Although not critical for approval due to the existing human experience, these data are necessary to assist in the extrapolation of the findings in the toxicology program to humans, as described in ICHS6.

CLINICAL REVIEW

Application Type	BLA
Submission Number	125276
Submission Code	0

Letter Date	November 19, 2007
Stamp Date	November 19, 2007
PDUFA Goal Date	September 18, 2008

Reviewer Name	Sarah Okada, M.D. SMO 7/31/08
Through	Jeffrey Siegel, M.D. JS 7/31/08 Clinical Team Leader
Review Completion Date	August 1, 2008

Established Name	Tocilizumab
(Proposed) Trade Name	Actemra®
Therapeutic Class	Interleukin-6 Inhibitor
Applicant	Hoffman-La Roche

Priority Designation	S

Formulation	Intravenous
Dosing Regimen	8 mg/kg every 4 weeks
Indication	Rheumatoid Arthritis (RA)
Intended Population	Moderately to Severely Active RA

TABLE OF CONTENTS

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

Recommend approval of this BLA with revisions to the proposed label, contingent upon resolution of CMC issues identified at inspection (see section 4.1 Chemistry Manufacturing and Controls).

1.2 Risk Benefit Analysis

Summary of Clinical Findings

Brief Overview of Clinical Program

Tocilizumab (TCZ) is a recombinant human monoclonal antibody targeting the interleukin 6 receptor (IL-6R). 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.

The data in this submission are derived from 5 randomized, double-blind controlled trials of TCZ in 4211 rheumatoid arthritis (RA) patients with moderately to severely active disease. Four were placebo-controlled trials (WA17822, WA17823, WA18062 and WA18063), and one was a non-inferiority trial (WA17824) comparing TCZ versus methotrexate (MTX). The trials studied the range of RA patients, from those with less refractory disease that had not previously required MTX (WA17824) to more typical RA patients who had inadequate response to MTX and other DMARDs (WA17822, WA17823, WA18063) and more refractory RA patients who had inadequate response to TNF inhibitors (WA18062). Three of the trials assessed TCZ vs. placebo as add-on therapy to background MTX (WA17822, WA17823, WA18062), one trial assessed TCZ vs. placebo as add-on therapy to a range of commonly used DMARDs including MTX (WA18063), and one trial assessed TCZ 8 mg/kg monotherapy vs. optimized MTX monotherapy (WA17824). Three of the trials also included a treatment arm with TCZ 4 mg/kg as add-on therapy (WA17822, WA17823, WA18062).

Summary of Efficacy

The primary endpoint for all studies was the proportion of ACR20 responders at Week 24. The primary comparison in each study was TCZ 8 mg/kg versus the study control group. In all four placebo-controlled trials, the proportion of patients achieving ACR20 response criteria at Week 24 in the TCZ 8 mg/kg group was higher than in the placebo group and the difference was statistically significant. Response rates ranged from 50 to

61% in the TCZ 8 mg/kg groups compared to rates of 10 to 27% in the placebo groups. Subgroup analyses by demographic characteristics, disease characteristics, and geographic region were consistent with the primary results; treatment with TCZ resulted in a higher proportion of ACR20 responders for all subgroups analyzed. In the primary analysis, missing data (e.g. if the patient discontinued the study or insufficient data were collected to calculate the ACR response for a patient) were imputed by classifying that patient as a non-responder with respect to the primary endpoint. Results of sensitivity analyses conducted using different imputation techniques were consistent with the primary analysis.

Study WA17824 compared TCZ 8 mg/kg monotherapy to optimized methotrexate monotherapy in MTX naïve patients and was designed as a non-inferiority trial. The pre-specified non-inferiority margin was 12%; that is, non-inferiority would be demonstrated if the lower limit of the 95% confidence interval (CI) of TCZ minus MTX was $\geq$ -0.12. This trial successfully demonstrated the non-inferiority of TCZ compared to MTX, as the lower limit of the 95% CI was +0.13. In the event of a demonstration of non-inferiority, the protocol specified a comparison of superiority. The results of this analysis demonstrated that the proportion of ACR20 responders in the TCZ group exceeded the proportion of ACR20 responders in the MTX group (71% vs. 52%, respectively), and the difference was statistically significant.

A total of 36 secondary endpoints were pre-specified, and the statistical analysis plan incorporated appropriate adjustments for multiplicity. Major secondary endpoints evaluated in this review include the proportion of ACR50 and ACR70 responders at Week 24, mean change from baseline to Week 24 in the individual ACR core variables, and the area-under-the-curve distribution of ACRn. Results for these secondary endpoints are consistent with the primary results and support the conclusion that TCZ is efficacious in the treatment of RA.

Summary of Safety

Four of the five pivotal RA studies were 24-week studies (WA17822, WA17824, WA18062, WA18063). Upon completing the 24-week controlled period, patients could continue open-label treatment with TCZ 8 mg/kg in long-term extension studies for up to 5 years. Study WA17823 is designed as a 2-year study (1st year double-blind, 2nd year open-label); 6-month interim data were submitted with this BLA. Six-month safety data from all 5 studies were pooled for an integrated analysis of safety by treatment groups. Almost 3800 patients have been exposed to TCZ in the Roche RA program, including placebo-treated patients who entered escape or open-label treatment. Over half of these patients have been exposed for up to 1 year, and almost 1500 have been exposed for up to 18 months. The majority of TCZ exposure has been to the higher dose of 8 mg/kg. Supportive safety data from trials conducted by Roche's co-development partner Chugai Pharmaceuticals were also reviewed.

During the 6-month controlled period, patients receiving TCZ 8 mg/kg + DMARD had the highest exposure-adjusted incidence of serious infections, approximately 5.7 serious infections per 100 patient-years exposure compared to 3.9 serious infections per 100 patient-years exposure in the placebo control group. Patients receiving TCZ 4 mg/kg + MTX also had a higher incidence of serious infections compared to placebo (4.7 serious infections per 100 patient-years), but the incidence was comparatively lower than with the TCZ 8 mg/kg combination therapy group. Patients on TCZ 8 mg/kg monotherapy did not have an elevated incidence of serious infections (3.2 serious infections per 100 patient-years). TCZ treatment was not associated with reactivation of latent tuberculosis (TB) infection during the clinical trials despite the lack of protocol mandated TB screening or prophylaxis and the world-wide distribution of study sites.

TCZ, when combined with DMARDs, was associated with an increased incidence of laboratory abnormalities, such as decreased white blood cell count (WBC) and platelets, elevations in lipid parameters, and most significantly, liver enzyme elevation. Changes in these parameters were temporally associated with TCZ treatment and resolved once treatment discontinued. Changes in WBC and platelets generally remained within the normal range. Increases in lipid parameters were on average small, but affected all parameters and total cholesterol/HDL ratio increased. Most liver enzyme abnormalities were transient and less than 3 times the upper limit of normal. Five percent of patients in the TCZ 8 mg/kg and 4 mg/kg combination therapy groups experienced at least one ALT elevation between 3 and 5 x ULN, compared to 4% of patients on MTX monotherapy and 1% of patients on placebo+ DMARD. The pattern of liver enzyme elevations was very similar in the methotrexate and TCZ 8 mg/kg monotherapy treatment arms of study 17824, where both monotherapy arms showed fewer instances of liver enzyme elevation compared to the tocilizumab combination treatment groups. However, TCZ 8 mg/kg monotherapy was associated with a higher rate of total bilirubin elevation to up to 3x ULN.

A single case meeting Hy's Law criteria (transaminase elevations >3 x ULN + bilirubin elevation > 2 x ULN without evidence of biliary obstruction) was identified in the TCZ global safety database and occurred on open-label TCZ 8 mg/kg with initiation of MTX after the patient completed 6-months of TCZ monotherapy without significant changes in transaminases. Abnormalities resolved with discontinuation of MTX and TCZ. Overall, in patients experiencing liver enzyme elevations who continued on study, modification of treatment regimen (a reduction of the dose of DMARD, an interruption of TCZ infusion and/or reduction of TCZ dose from 8 mg/kg to 4 mg/kg) led to a decrease or normalization without subsequent elevation of liver enzymes or occurrence of hepatobiliary AEs. Currently available data on over 3700 patients treated with TCZ for up to 2 years contain no clinical events of hepatitis or hepatic failure.

Malignancies occurred at similar rates in the TCZ groups as in the placebo group during the 6-month controlled period. These rates ranged from 1.5 to 1.6 malignancies per 100 patient-years and were slightly higher than published background rates in RA patients

(1.3-1.4 per 100 patient-years). Based on interim data submitted from the long-term extension studies, malignancy rates have not risen over the extended duration of exposure in these trials.

During the 6-month controlled period, 3 gastrointestinal (GI) perforation events occurred in the TCZ 8 mg/kg treatment groups compared to none in the placebo or TCZ 4 mg/kg per treatment groups. Overall, GI perforations were uncommon, a total of 16 events occurred in the TCZ global RA program through data cut-off, which includes approximately 4700 patients and over 7900 patient-years of exposure. Four cases of demyelinating adverse events were also observed in the global RA program.

Overall, the safety data from the Roche pivotal trials and long-term extensions, and the global experience with TCZ depict the profile of an immunosuppressant, with its inherent risks, such as serious infections. TCZ manifested effects on laboratory parameters, such as decreased white blood cell count, increases in lipids, and most significantly, liver enzyme elevation, although these were not associated with clinical adverse events in the controlled setting of the clinical trial experience. Malignancies, GI perforations, and demyelinating adverse events were observed in the clinical trials, however the relative risk and role of TCZ treatment in the development of these adverse events is not well defined. These types of potential risks are not unique in the RA therapeutic armamentarium and have historically been handled via appropriate labeling, which should also be adequate in this case. The clinical trial experience has been extensive, but may not capture the full extent of safety concerns that may arise with long-term IL-6 inhibition.

Risk-Benefit Overview

Table 1 below describes an estimate of the potential benefit vs. potential risks of TCZ treatment in RA. Number-needed-to-treat/-harm (NNT/NNH) calaculations were based on the 4 placebo-controlled studies, utilizing the comparison of TCZ 8 mg/kg + DMARD vs. placebo + DMARD from the 6-month controlled period. Based on average proportion of responders in these studies, as few as 3 patients would need to be treated to have at least one patient experiencing a benefit on the level of an ACR20 response, and as few as 7 patients would need to be treated to have at least one patient experiencing a benefit of the magnitude of an ACR70 response.

During this period, the frequency of malignancy diagnoses and lipid-lowering agent starts was the same in the TCZ 8 mg/kg + DMARD group as for the placebo + DMARD group, resulting in a NNH of ∞. As a caveat, it should be noted that the proportion of patients experiencing malignancy, SAE, SIE, or needing to start lipid lowering agents all increased over the duration of the long-term extension studies. However, exposure-adjusted incidence of malignancies remained similar to the controlled period, and exposure-adjusted incidence of serious infections was lower. The rate of GI perforations

may be slightly elevated over background rates in RA but were still an uncommon occurrence.

Table 1: Risk-Benefit Overview

Risk-Benefit Overview		
Clinical Activity	Proportion Responding	Number Needed to Treat
ACR20	58%	~3
ACR50	36%	~4
ACR70	18%	~7
Risks	Frequency	Number Needed to Harm
Serious Infection	5.7 per 100 pt-yrs	~56
Malignancy	1.5 per 100 pt-yrs	∞
GI Perforations	0.2 per 100 pt-yrs	~385
Demyelinating AE	.05 per 100 pt-yrs	n.d.[a]
Liver enzyme abnormalities[b]	18 per 100 pt-yrs	~7
Lipid lowering agent starts	2.8 per 100 pt-yrs	∞

Data presented pertains to TCZ 8 mg/kg + DMARD group
NNT/NNH calculations based on comparison with placebo + DMARD, controlled period, exposure adjusted
a) not determinable-one event occurred during a placebo-controlled period, but tx remains blinded
b) based on most common "marked abnormality" of elevated ALT; no clinical hepatotoxicity events noted

Liver enzyme abnormalities were relatively common. In most cases liver enzyme elevations were mild to moderate; no cases of clinically evident hepatoxicity occurred, and abnormalities resolved with discontinuation of treatment. However, a single case of a patient meeting Hy's Law criteria was observed in approximately 4700 patients in the TCZ global RA program. This case was confounded by the concomitant initiation of relatively high dose MTX and may not reflect the risk of TCZ alone. Nonetheless, using the estimate of severe drug-induced liver injury as occurring at 1/10th the rate of Hy's Law cases, 1 case of severe liver injury might be expected in 47,000 treated patients.

Overall, the risk:benefit profile of TCZ in RA appears to be favorable, with many more patients potentially benefiting from treatment compared to those at potential risk. Although the potential for severe liver injury exists, particularly with the combination of TCZ and MTX, the relatively extensive clinical experience to date suggests that irreversible or clinically evident hepatotoxicity may be avoidable with sufficient monitoring and appropriate dose modification, since neither was observed in the studies.

1.3 Recommendations for Postmarketing Risk Management Activities

A Risk Evaluation and Mitigation Strategy (REMS) is warranted and should include:
1) Monitoring and dose modification recommendations for absolute neutrophil count, platelet count and liver enzymes

- Monitoring at 4-8 week intervals, with modification or interruption of TCZ dosing as per instructions to be specified in labeling.

2) MedGuide

- To assure communication to patients of the risks of tocilizumab treatment, including serious infections, GI perforations, and necessity of laboratory monitoring

1.4 Recommendation for other Postmarketing Study Commitments

1) Long-term observational safety studies
The intent of long-term safety studies is to identify delayed adverse events that may not readily manifest in the shorter duration of controlled clinical trials. The applicant has two ongoing long-term extension studies (WA18695/WA18696) that will allow for observation of patients with up to 5-years treatment. Patients completing the core studies were eligible to continue treatment in these extensions; as of the data cut-off for this submission, over 2500 patients have enrolled. Based on past experience with other biologics, these studies should be of sufficient size and duration to characterize most of the key adverse events of interest.

2) Registry
To better define the risk of treatment with respect to cardiovascular events, a cohort of TCZ-treated patients should be enrolled into an established registry that includes patients on other RA treatments who could serve as an internal control. This cohort will need to be of sufficient size, and the observation period of sufficient duration, to detect an increased relative risk over the background rate and also to detect the delayed risk that may be associated with adverse changes in lipids, as these changes would not be expected to have a short-term adverse effect on cardiovascular risk. A registry cohort would also offer the potential for further characterization of other adverse events of interest such as GI perforations, serious infections and clinical hepatotoxicity, and further characterization of the safety profile of tocilizumab in subpopulations of patients who were not highly represented in the pivotal studies—more patients over 75 and with important comorbidities.

3) Immunization studies
For products intended to suppress the immune response, such as tocilizumab, it is beneficial to know how the treatment might impact the response to immunization, in order to better inform clinicians how to handle desired immunizations for their patients; e.g., whether patients should be brought up to date on immunizations before starting treatment, and whether treatment must be interrupted to achieve adequate responses to future immunizations. The applicant currently has such a study planned as a substudy of the long-term extension studies currently in progress.

4) Studies to achieve compliance with PREA
Polyarticular juvenile idiopathic arthritis (PJIA) is considered to be the pediatric equivalent of adult RA. Therefore, in accordance with the Pediatric Research Equity Act (PREA) of 2003, studies in PJIA are mandated. With this submission, the applicant has requested a deferral for patients age 2-17 with PJIA, and a waiver for children 0-2, since

PJIA is extremely rare in this age group. These requests have been granted for other therapeutic biologics, as, for ethical reasons, it is desirable to have an adequate experience with the safety profile of a treatment in adults before proceeding with extensive studies in children. The applicant has already discussed details of their proposed Phase 3 program in PJIA and systemic juvenile idiopathic arthritis (SJIA) with the Agency. The proposed PJIA study is a 12-week randomized, double-blind placebo-controlled study (with option for early escape) in 130 patients with active disease. This study is planned to commence enrollment in the 4th quarter of 2008, with submission of the final study report planned for 2012. The proposed study appears adequate to meet the requirements of PREA.

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). 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. 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. The molecular mass of the protein moiety of the antibody is approximately 145 kDa. The tocilizumab drug product comes in 80 mg, 200 mg, and 400 mg vials at 20 mg/mL concentration. All three strengths are a sterile, colorless to pale yellow, preservative-free liquid and are identical in qualitative and quantitative composition (dose-proportional), differing only with respect to fill volume (4 ml, 10 ml, and 20 ml, respectively). The concentrate is to be diluted to 100 mL in 0.9% sodium chloride solution for intravenous infusion prior to administration. Administration is as a single intravenous drip infusion over 1 hour.

If approved, TCZ would be the first IL-6 inhibitor approved for use in the United States. The applicant proposes a dose of 8 mg/kg IV every 4 weeks for the rheumatoid arthritis (RA) indication.

Roche's co-development partner, Chugai Pharmaceutical Co. Ltd., received approval in Japan in April 2005 for the use of tocilizumab in the treatment of multi-centric Castleman's Disease. In April 2008, tocilizumab was approved in Japan for the treatment of adult RA, systemic juvenile idiopathic arthritis (SJIA) and polyarticular juvenile idiopathic arthritis (PJIA).

2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)

Table 2 below lists the currently available approved treatments for RA. These include the three currently approved TNF inhibitors infliximab, etanercept, and adalimumab, one interleukin 1 antagonist (anakinra), one B-cell depleting therapy (rituximab, an anti-CD20 monoclonal antibody), and one T-cell costimulation modulator (abatacept, a CTLA4-Ig fusion protein). The remaining drugs on this list are small molecules with various mechanisms of action.

Table 2 FDA-approved drugs/biologics for RA

FDA-approved drugs/biologics for RA		
Drug Name	**Approved for RA***	**Current** Indicated Population and Claims**
sulfasalazine	date unknown	RA with inadequate response to salicylates or other NSAIDs
methotrexate	10/31/1988	Patients with severe, active RA who have had insufficient response to, or are intolerant of, NSAIDs
hydroxychloroquine	date unknown	RA
azathioprine	date unknown	Active RA, to reduce signs and symptoms
penicillamine	date unknown	Severe, active RA who have failed to respond to conventional therapy
cyclosporine	5/22/1997	Severe, active RA with inadequate response to MTX
auranofin	date unknown	Adults with active RA who have had insufficient response to, or are intolerant of, NSAIDs
leflunomide	9/10/1998	Adults with active RA, to reduce signs and symptoms, inhibit structural damage, and improve physical function
etanercept	11/2/1998	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA
infliximab	11/10/1999	In combination with MTX, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA
anakinra	11/14/2001	Reducing signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patient ≥18 years old who have failed 1 or more DMARDs
adalimumab	12/31/2002	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adults with moderately to severely active RA
abatacept	12/23/2005	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adults with moderately to severely active RA who have had inadequate response to one or more DMARDs
rituximab	2/28/2006	In combination with MTX, for reducing signs and symptoms in adult patients with moderately to severely active RA who have had inadequate response to one or more TNF antagonist therapies

* Approval dates can only be verified from 1984 to the present
**Approved label as of 11/28/2007
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
http://dailymed.nlm.nih.gov/dailymed/about.cfm
http://cdemet.cder.fda.gov/ogd/da/Da.htm

2.3 Availability of Proposed Active Ingredient in the United States

Tocilizumab is not currently available in the United States.

2.4 Important Issues With Consideration to Related Drugs

Tocilizumab is an IL6 inhibitor, and if approved, would be the first in class; therefore the safety profile of IL6 inhibition is based on the information in this BLA and anticipated effects based on currently available knowledge about the biological effects of IL6 and the clinical trial experience with tocilizumab. Based on this information, the primary issues of concern pertain to overall immunosuppression and the risk for serious infection, liver enzyme abnormalities and concern that this could result in clinically evident hepatotoxicity, reduction in white blood cell counts and incumbent risk for infection from this, and elevated lipids with whatever long-term ramifications this may have on cardiovascular risk. As IL6 is the primary driver of acute phase reactants, and inflammation is associated with increased cardiovascular risk, it is also possible that inhibition of IL6 may be beneficial with respect to cardiovascular risk. Basic science literature suggests IL6 may have a promotional effect on certain malignancies, and therefore inhibition of IL6 could have a protective effect. However, the clinical trial evidence thus far suggest a neutral effect with respect to tocilizumab treatment and malignancy overall.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

The Phase 1/Phase 2 program (including dose-ranging studies) was conducted in Europe and Japan by Roche's co-development partner Chugai Pharmaceuticals. Roche's initial US regulatory contact was via a Pre-IND/End of Phase 2 (EOP2) meeting September 9, 2004 with the FDA Division of Therapeutic Biologic and Internal Medicine Products (DTBIMP). At this meeting, the applicant and the Agency came to agreement regarding the size and duration of the safety database, safety-related monitoring and toxicity stopping rules, additional analyses by body weight, use of blinded/independent joint assessors (due to anticipated treatment-related changes in laboratory evaluations) and primary and secondary endpoints for the pivotal trials. The Agency agreed with the applicant's proposed primary endpoints of ACR20 at week 24 for the signs and symptoms claim and change from baseline to week 52 in total Sharp score to support the structural damage claim. The Agency recommended that analyses of health assessment questionnaire (HAQ) data be provided as a responder analysis (e.g., the proportion of patients experiencing a >0.3 u improvement at 6 and 12 months) rather than as an area-under-the-curve (AUC) analysis to support the physical function claim. The applicant plans to submit the full package to support claims for major clinical response, inhibition of the progression of structural damage, and improvement in physical function subsequent to this original BLA submission. The Agency also provided recommendations for the Statistical Analysis Plan (e.g. use of sequential testing of endpoints, maintaining a 2-sided test with α=0.05 to conserve the overall alpha) and requested justification for the applicant-proposed non-inferiority margin of 12%.

The Agency provided additional comments regarding the data reporting and analysis manual (DRAM) by teleconference September 8, 2005, and regarding the Statistical Analysis Plan (SAP) in November 2006. Expectations for BLA format and content were relayed in May 2007, and analyses for the BLA were agreed upon in a pre-BLA meeting September 2007.

2.6 Other Relevant Background Information

As mentioned above, tocilizumab has been approved in Japan for Castleman's Disease, RA, SJIA, and PJIA. Due to the recent timing of the approval for the latter 3 indications, this submission only included the translated Japanese label for tocilizumab for Castleman's Disease. The approved dose and regimen for Castleman's Disease is 8 mg/kg every 2 weeks. The label includes recommendations for monitoring of C-reactive protein (CRP) at each administration, WBC and platelet count at each administration for 1 month then monthly thereafter, monthly total cholesterol and triglyceride levels for 3 months, then every 3 months thereafter, and immunoglobulin monitoring every 3 months.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The BLA submission was in electronic common technical document format and was adequately organized. The Division of Scientific Investigations (DSI) was consulted to conduct routine sponsor/monitor inspection for a new molecular entity. The inspection audited all 5 studies, WA17822, WA17823, WA17824, WA18062 and WA18063, and focused on 2 US investigators and 3 Mexican investigators who were among the highest enrollers of patients.

The inspection reviewed the following: quality assurance and clinical operations, study monitoring procedures, records and reports, informed consents, participating clinical investigators, monitoring reports, case report forms (CRFs), data collection, and study drug accountability. The inspector also compared selected subjects with the firm's data listings. An audit of 20 subjects' records, out of a total of 4211 enrolled, was conducted. A Form FDA 483, Inspectional Observations, was issued at the end of inspection. Hoffman-LaRoche responded to the items listed on the Form 483 in letters dated 06/05 and 07/02/2008. DSI's conclusions were that the studies appeared to have been conducted adequately, and that the data submitted by the applicant may be used to support the respective indication.

No contract research organizations (CROs) were used to conduct the Roche pivotal RA trials. The 5 studies were conducted and monitored according to Roche standard operating procedures (SOPs) and guidelines. Data recorded on paper case report forms

(CRFs) were verified by study monitors at each scheduled monitoring visit according to a Source Document Verification Plan developed by the Study Management Teams. Findings of the monitoring visits (including resolutions and actions taken) were documented on a Monitoring Report Form and signed by the Roche Country Study Manager or designee. Investigators received training at several points during the program, utilizing study tools and meetings.

3.2 Compliance with Good Clinical Practices

The applicant certified that all clinical investigations in the BLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 11972 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

DSI inspection revealed no violations pertaining to compliance with GCP.

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 (v.4/06) certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified. DSI inspection found deficiencies in prompt and complete financial disclosure documentation, however also concluded that the applicant had taken appropriate corrective actions in response to the Form 483 findings.

4 Significant Efficacy or Safety Findings Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Primary FDA CMC reviewer: Gerald Feldman, Ph.D.

Review of the data in this submission by Dr. Gerald Feldman confirmed that tocilizumab interferes with ligand binding to the receptor and no effector functions were demonstrated. Four manufacturing process generations (G1-G4) have been utilized during the clinical development program; comparability of the resulting drug substance and drug product has been confirmed. Only product made via the G4 process was utilized for the Phase 3 trials submitted in this application. Pharmacokinetic (PK) and immunogenicity assays were determined to be adequately validated. Although the CMC review is still pending at the time of this review, Dr. Feldman reports that the CMC data in this BLA and its amendments are adequate to support approval.

However, major site inspection findings were noted on inspection of the Utsunomiya facility (May 21-June 5, 2008) that may affect the approvability of this product. These issues include:

- Facility
  - [redacted] equipment in the drug substance facility (UT-1 and UT2) up to May 2008. b(4)
  - Insect infestation
  - Inadequate EM
  - Inadequate facility cleaning and disinfection
  - [redacted] b(4)
  - Inadequate testing of [redacted]
  - Lack of adherence to validation protocols
  - Inadequate equipment cleaning
- Quality System:
  - Misrepresentation of sterility assurance information in the BLA
  - Lack of personnel training in US GMP regulations (21CFR 211) and Q7
- Production and Process Controls
  - Inadequate sterility assurance data
    - [redacted] b(4)
  - Inadequate media fill program
    - Not all worst-case simulations conducted
    - Inadequate oversight
  - Hold time for buffer, column storage solution and drug substance intermediates not validated from a microbial control perspective
  - Inadequate record keeping

At the time of this review, the applicant is in the process of correcting these deficiencies and formulating a risk assessment pertaining to the use of the [redacted] and submitting responses to the inspection finding to the BLA. These must be reviewed and determined adequate before the BLA can be approved. b(4)

4.2 Clinical Microbiology

Data on microbial and viral controls and viral and non-viral adventitious agents was reviewed by CMC and determined to be acceptable. However inspection findings (see section 4.1) raise concerns about the integrity of the sterility assurance data.

4.3 Preclinical Pharmacology/Toxicology

Primary pharmacology/toxicology reviewer: Asoke Mukherjee, Ph.D.

The results of the tocilizumab nonclinical development program are described in Table 3 below. The primary toxicities noted in the animal studies included a small amount of hepatic granuloma formation and foci of skeletal muscle degeneration. In pre-submission regulatory activities, the Agency agreed to waive carcinogenicity and segment III

reproductive toxicology studies. As therapeutic biologic products are macromolecules that do not enter the nucleus and are unlikely to affect DNA, these products have historically not been considered to present a high risk for carcinogenicity. Concerns regarding carcinogenicity may otherwise be related to the normal biologic activities of IL6, and therefore the effect of inhibition, if the cytokine is important for protective homeostatic mechanisms. In fact, the literature suggests that IL6 is pro-proliferative and anti-apoptotic in several different animal models of cancer, including mouse models of myeloma, colitis associated cancer, and hepatocellular carcinoma [Naugler and Karin, 2008]. Therefore inhibition of IL6 might theoretically be expected to reduce or impede the development of certain malignancies.

Table 3: Nonclinical Overview

Overview of the Nonclinical Development Program	
Type of Study	Significant Results
Pharmacology	Primary pharmacodynamics and tissue cross reactivity
Safety Pharmacology	Appropriate organ safety studies were conducted; no significant findings
Pharmacokinetics/ADME Rat and Monkey	Plasma and urine levels in monkeys, ADME in both $T_{1/2}$ monkeys 10-13 days
Acute Toxicology Rat and Monkey	Negative up to 100 mg/kg single dose in monkeys
Repeat Dose Toxicology Rodent 1-month Monkey 6-months	No systemic toxicity up to 50 mg/kg/day; injection site reactions Anti-TCZ antibodies noted at 1 and 10 mg/kg; liver granuloma, skeletal muscle degeneration, and gingival inflammation noted at 10 and 100 mg/kg
Genetic Toxicology Ames mutagenicity In vitro clastogenicity In vivo	 Negative Negative Not required due to lack of membrane transport
Carcinogenicity Mouse and Rat	Waived.
Reproductive Toxicology Segment I: Rat Segment II: Rat Rabbit Monkey Segment III	 No effect on male or female fertility up to 50 mg/kg/day No effect on organogenesis; no maternal toxicity at up to 50 mg/kg/day Anti-TCZ antibodies noted at all doses; reduced sternum development at all doses; higher rate of fetal death at mid-dose of 5 mg/kg/day Higher incidences of abortion and fetal deaths noted at 2 highest doses of 10 and 50 mg/kg/day; no teratogenicity noted Waived

Source: Described results of studies from pharm-tox review by Dr. Asoke Mukherjee

IL6 knock-out mice develop normally, suggesting that IL6 would not be essential for normal fetal development. However, these mice demonstrate an increased susceptibility to infection, with defects in T-cell dependent antibody production, and lack of ability to produce an acute-phase response, as would be expected given what is known about the roles of IL6. Lacking evidence of reproductive toxicity in knock-out mice and other evidence that could implicate an essential role of IL6 in embryofetal development, segment III reproductive toxicity studies were similarly waived for tocilizumab in pre-submission regulatory meetings with the applicant.

Because IL6 is a pleiotropic cytokine, with a potential role in numerous processes, not all of which are pro-inflammatory, pro-proliferative, or anti-apoptotic, the primary pharmacology-toxicology reviewer, Dr. Asoke Mukherjee expressed concerns that it may be theoretically possible that IL6 could play a protective role against malignancy via some of these other pathways and that inhibition of IL6 could be deleterious. Therefore it is his opinion that carcinogenicity studies should be required for approval.

After surveying the literature, it is this reviewer's opinion that more evidence exists to implicate a pathologic role of IL6 and malignancy, rather than a protective role, at least for the types of malignancies in which this has been investigated. Ultimately, only long-term clinical data can answer this question definitively, and animal carcinogenicity studies will likely not contribute significantly to an understanding of how IL6 inhibition might affect malignancy development in humans. The applicant has provided extensive human data from the clinical trial program to date, and long-term data continues to accrue. These data thus far are not conclusive; patients on TCZ treatment appear to have similar exposure-adjusted incidence rates of malignancy as patients on placebo + DMARD.

4.4 Clinical Pharmacology

Much of this section has been excerpted and adapted from the clinical pharmacology review by Dr. Lei Zhang.

4.4.1 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.

4.4.2 Pharmacodynamics

IL-6, sIL-6R, and C-reactive protein (CRP) were monitored n multiple studies as pharmacodynamic (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 reflects inflammatory activity in RA and, along with erythrocyte sedimentation rate (ESR), is used in various disease activity indices to include the disease activity score 28 (DAS28) and American College of Rheumatology (ACR) response criteria.

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.

Pharmacokinetics

Population-pharmacokinetic (POP-PK) analysis was conducted based on data obtained from 4 Phase 3 studies. Clearance (CL) was described by a 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.

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 applicant 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 applicant 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 creatinine clearance, CLcr).

***Exposure-Response (ER)*:**
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 these data, 4 and 8 mg/kg were selected for studying in Phase 3 studies. See section 6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations, for further details.

ER for Efficacy: In the pivotal RA studies, both 4 and 8 mg/kg every 4 week doses showed statistically significant increases in ACR20 response compared to placebo at Week 24. A higher proportion of patients achieved ACR20 with 8 mg/kg doses than with

the 4 mg/kg dose. See section 6.1.5 Analysis of the Primary Endpoint(s), for further details.

ER for Safety: Although there did not appear to be an overall correlation of adverse events and 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. See section 7.5.1 Dose Dependency for Adverse Findings, for further details.

Immunogenicity: A small proportion of patients developed anti-TCZ antibodies during the clinical trials or long-term extensions. See section 7.4.6 Immunogenicity, for further details. Immunogenicity did not appear to have an effect on PK, based on a limited number of samples.

Drug-Drug Interactions: IgG antibodies are not metabolized by cytochrome P450 enzymes. 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 is plausible.

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 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 the reverse of down-regulation of CYP2C19. Although TCZ showed little effect on the exposure of dextromethorphan, the exposure of dextrorphan (a CYP2D6 metabolite of dextromethorphan) level decreased. Dextrorphan undergoes further metabolism by CYP3A4.

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

Drug interactions may have clinical implications 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) and

where a decrease of up to 50% could become clinically relevant. In addition, depending on the P4503A4 level change, a decrease in oral contraceptive (CYP3A4) exposure is plausible and may lead to decrease in efficacy.

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

5 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

The U.S. biologics license application (BLA) is comprised of 5 controlled studies. The key design features of these studies are summarized in Table 4, below.

Table 4: Key Design Features of the 5 Pivotal Phase 3 Studies and the 2 Open-Label Extensions

	WA17822	WA17823	WA17824	WA18062	WA18063	WA18695	WA18696
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	OL extension study: approximately 5 years*	OL extension study: approximately 5 years*
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	Patients completing treatment in WA17822	Patients completing treatment in WA17824, WA18062, WA18063, WP18663
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 <u>or</u> 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)	**1 arm:** Tocilizumab: 8 mg/kg iv every 4 weeks plus MTX	**1 arm:** Tocilizumab: 8 mg/kg iv every 4 weeks alone or plus MTX / other 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	537**	1902**
Primary Endpoint at Week 24	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	Long term safety/efficacy	Long term safety/efficacy

DB = double blind. R = randomized. PC = placebo controlled, DD = double dummy. OL = open label
* Or when tocilizumab becomes commercially available in the participating country. or when the sponsor decides to discontinue the study.
** Patients were not randomized into WA18695 and WA18696. but enrolled from studies WA17822. WA18063, WA18062 and WA17824

Applicant Table 1 of Module 2.7.3 Summary of Clinical Efficacy

5.2 Review Strategy

With regard to efficacy, each of the 5 pivotal studies was reviewed individually for the primary endpoint of ACR20 response at Week 24 and key secondary endpoints, such as ACR50 and ACR70 responses at Week 24, change from baseline to Week 24 in ACR core variables, and time course of ACR20 and ACR50 responses. Sensitivity analyses of the primary endpoint were also performed for each individual study. Studies WA17822,

WA17823, and WA18063 were pooled for integrated analyses of efficacy and subgroup analyses, as these studies had similar designs and enrolled a similar target population of RA patients with inadequate response to DMARDs, including MTX. Of note, WA17823 is designed as a 1-year double-blind study with a 2nd year open-label period, but interim analyses at Week 24 were submitted for this BLA.

To facilitate evaluation of uncommon adverse events and better understanding of the safety profile across the entire range of RA patients studied, the 5 pivotal studies were pooled and integrated safety results displayed by treatment group for the 6-month safety population. Interim safety results for the long-term open-label extension studies are also assessed in the integrated review of safety. Safety data from supportive studies in the Chugai program were evaluated with respect to deaths, serious adverse events, and other adverse events of interest.

5.3 Discussion of Individual Studies

WA17822
Study WA17822 is a 24-week randomized, double-blind, placebo-controlled study in 623 patients with moderately to severely active RA with previous inadequate clinical response to MTX at a dose of at least 10-25 mg per week. This study was conducted entirely outside the US, at 73 centers in 17 countries worldwide.

Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks, given in addition to background treatment with MTX 10 to 25 mg (stable dose) weekly. Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy (TCZ 8 mg/kg + MTX) at weeks 16 and 20.

The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the week 24 visit, all patients (including escape patients) could roll-over into an open-label long-term extension study (WA18695) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years.

WA17823
Study WA17823 is a 2-year (1st year double-blind, 2nd year open-label) randomized, double-blind, placebo-controlled study in 1196 patients with moderately to severely active RA with previous inadequate clinical response to MTX at a dose of at least 10-25 mg per week. This study is being conducted at 137 centers in 15 countries; 58 sites are in the US, and the total US patient population is 332 (28% of the total study population).

Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks, given in addition to background treatment with MTX 10 to 25 mg (stable dose) weekly. Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue unchanged for the initial 24 weeks of the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy. Because the study is to remain blinded through Week 52, patients entering escape at week 16 were assigned doses in an automated fashion using the Interactive Voice Response System (IVRS). Those patients initially assigned to receive 4 mg/kg or 8 mg/kg TCZ were assigned to receive 8 mg/kg TCZ as escape treatment; patients initially assigned to placebo were assigned to receive 4 mg/kg TCZ as escape treatment. If after 3 doses or more of this escape therapy (which would occur after Week 24, and is therefore not germane to the interim data submitted in this BLA), patients who continued to show less than 20% improvement from baseline in both SJC and TJC would undergo another escape step whereby they would receive 8 mg/kg TCZ as open-label treatment.

The primary endpoint for the interim analysis submitted was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. For this interim analysis, only the study statistician was involved in the unblinding and analysis of the data post database lock, and this person was removed from the conduct of the ongoing study. The study will be fully unblinded for the radiographic analysis at Week 52.

WA17824

Study WA17824 is a 24-week randomized, double-blind, parallel group non-inferiority study in 673 patients with moderately to severely active RA who had not been treated with MTX within 6 months prior to randomization, and who had not discontinued previous MTX treatment due to toxicity or lack of response. This study was conducted at 120 centers in 18 countries; 54 sites were in the US and the total US patient population was 211 (31% of the total).

Patients were randomized 1:1 to receive either TCZ 8 mg/kg IV every 4 week plus placebo MTX capsules or MTX oral capsules weekly plus placebo IV infusion every 4 weeks. MTX was provided in an escalating dose regimen starting at 7.5 mg weekly, increasing to 15 mg weekly at Week 4, then to 20 mg weekly at Week 8. Stable NSAID and corticosteroid (≤10 mg/day prednisone equivalent) were continued throughout the study. As an internal control for efficacy, some patients at centers in Canada, Israel, and the US were enrolled into a placebo-controlled substudy whereby they would receive 8 weeks total of placebo capsules and placebo IV infusions. At Week 8, patients received TCZ 8 mg/kg plus placebo MTX capsules for the remaining 16 weeks of the study. Only patients in this placebo-controlled substudy were eligible for escape treatment (to open-label TCZ 8 mg/kg) if they experienced a 20% increase in the number of active swollen and tender joints at any of the first 7 weekly visits.

The primary efficacy analysis, performed on the per-protocol population, was a non-inferiority comparison (pre-specified non-inferiority margin of 12%) of the proportion of ACR20 responders at Week 24 in the MTX group versus the TCZ 8 mg/kg group. If TCZ was shown to be non-inferior to MTX in ACR20 response at Week 24, testing for superiority was pre-specified.

After the completion of 24 weeks of randomized treatment, patients could either enter a "Transition Phase" or roll over to an open-label, long-term extension study (WA18696) in which they would receive TCZ 8 mg/kg every 4 weeks for up to 5 years. Patients who achieved a ≥50% decrease in the number of active swollen and tender joints (compared to baseline) while receiving their current blinded study treatment at both Week 20 and Week 24 had the option of continuing their current blinded study treatment until the last patient enrolled into the study and the study database had been locked. Patients not maintaining this level of improvement could immediately enroll in WA18696 and receive open-label TCZ treatment. Approximately 101 patients entered the transition phase.

WA18062
Study WA18062 is a 24-week randomized, double-blind, placebo-controlled study in 499 patients with moderately to severely active RA with previous inadequate clinical response to, or who were intolerant of, treatment with one or more TNF inhibitor therapies within one year prior to randomization. This study was conducted at 128 centers in 13 countries; 70 sites were in the US, and the total US patient population was 258 (52% of the total).

Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks, given in addition to background treatment with MTX 10 to 25 mg (stable dose) weekly. Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy (TCZ 8 mg/kg + MTX) at weeks 16 and 20.

The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the week 24 visit, all patients (including escape patients) could roll-over into an open-label long-term extension study (WA18696) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years.

WA18063
Study WA18063 is a 24-week randomized, double-blind, placebo-controlled study in 1220 patients with moderately to severely active RA with previous inadequate clinical response to current non-biologic DMARDs, including MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide. This

study was conducted at 130 centers in 18 countries; 64 sites were in the US, and the total US patient population was 498 (41% of the total).

Patients were randomized (2:1) to receive TCZ 8 mg/kg IV every 4 weeks or placebo IV every 4 weeks, in addition to background treatment with their current DMARD(s). Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy (TCZ 8 mg/kg + MTX) at weeks 16 and 20.

The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the week 24 visit, all patients (including escape patients) could roll-over into an open-label long-term extension study (WA18696) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years.

6. INTEGRATED REVIEW OF EFFICACY

Summary of Efficacy Results and Conclusions

The primary endpoint for all studies was the proportion of ACR20 responders at Week 24. The primary comparison in each study was TCZ 8 mg/kg versus the study control group. In all four placebo-controlled trials, the proportion of patients achieving ACR20 response criteria at Week 24 in the TCZ 8 mg/kg group was higher than in the placebo group and the difference was statistically significant. Response rates ranged from 50 to 61% in the TCZ 8 mg/kg groups compared to rates of 10 to 27% in the placebo groups. Subgroup analyses by demographic characteristics, disease characteristics, and geographic region were consistent with the primary results; treatment with TCZ resulted in a higher proportion of ACR20 responders for all subgroups analyzed. In the primary analysis, missing data (e.g. if the patient discontinued the study or insufficient data were collected to calculate the ACR response for a patient) were imputed by classifying that patient as a non-responder with respect to the primary endpoint. Results of sensitivity analyses conducted using different imputation techniques were consistent with the primary analysis.

Study WA17824 compared TCZ 8 mg/kg monotherapy to optimized methotrexate monotherapy in MTX naïve patients and was designed as a non-inferiority trial. The pre-specified non-inferiority margin was 12%; that is, non-inferiority would be demonstrated if the lower limit of the 95% confidence interval (CI) of TCZ minus MTX was ≥ -0.12. This trial successfully demonstrated the non-inferiority of TCZ compared to MTX, as the lower limit of the 95% CI was +0.13. In the event of a demonstration of non-inferiority, the protocol specified a comparison of superiority. The results of this analysis demonstrated that the proportion of ACR20 responders in the TCZ group exceeded the

proportion of ACR20 responders in the MTX group (71% vs. 52%, respectively), and the difference was statistically significant.

A total of 36 secondary endpoints were pre-specified, and the statistical analysis plan incorporated appropriate adjustments for multiplicity. Major secondary endpoints evaluated in this review include the proportion of ACR50 and ACR70 responders at Week 24, mean change from baseline to Week 24 in the individual ACR core variables, and the area-under-the-curve distribution of ACR response, ACRn. Results for these secondary endpoints are consistent with the primary results and support the conclusion that TCZ is efficacious in the treatment of RA.

6.1 Proposed Indication

The proposed indication for TCZ is for reducing signs and symptoms of RA in adult patients with moderately to severely active rheumatoid arthritis, when used alone or in combination with MTX or other DMARDs. (Paraphrased from the applicant's proposed wording.)

6.1.2 Methods/Study Design

Efficacy data from all 5 pivotal trials were used to support the proposed indication, as these trials represent the full range of RA patients with moderately to severely active disease who would potentially be treated with TCZ. Study WA18062 enrolled patients who could be considered more refractory, having had inadequate response to TNF inhibitors. Study WA17824 enrolled RA patients who could be considered as having early or less refractory disease, since these patients were not receiving DMARDs such as MTX at the time of enrollment. This study also provided the primary evidence for the utility of TCZ monotherapy. Study WA18063 enrolled patients taking the more commonly prescribed biologic DMARDs, allowing assessment of TCZ treatment when added to a range of DMARDs, as might be expected in clinical practice. Studies WA17822 and WA17823 allow for assessment of the most common anticipated clinical scenario of TCZ when added to background MTX. For additional details of these studies, refer to section 5.3 Discussion of Individual Studies, above and section 9.4 Individual Study Reports, below.

6.1.3 Demographics

Table 5 Baseline Demographics and Disease Characteristics

Integrated Summary of Baseline Demographics and Disease Characteristics (ITT populations/PP population of WA17824)								
	Pooled DMARD Inadequate Responders*			TNF Inadequate Responders (WA18062)			Early RA (WA17824)	
	Placebo + DMARD** n = 1010	TCZ 4mg/kg + DMARD** n = 612	TCZ 8 mg/kg + DMARD** n = 1406	Placebo + MTX n = 158	TCZ 4mg/kg + MTX n = 161	TCZ 8 mg/kg + DMARD** n = 170	MTX n = 259	TCZ 8 mg/kg n = 265
Gender								
Female	833 (82)	511 (83)	1154 (82)	125 (79)	130 (81)	143 (84)	211 (81)	219 (83)
Male	177 (18)	101 (17)	252 (18)	33 (21)	31 (19)	27 (16)	48 (19)	46 (17)
Age (years)								
mean	52.1	51.4	52.8	53.4	50.9	53.9	50.1	51.1
Height (cm)								
mean	162.7	162.0	162.5	164.8	165.0	164.1	163.0	162.3
Weight (kg)								
mean	73.2	72.1	72.6	75.4	76.4	74.3	72.6	73.4
Race								
White	724 (72)	439 (72)	406 (29)	150 (95)	144 (89)	152 (89)	188 (73)	187 (71)
Asian	88 (9)	42 (7)	127 (9)	1 (<1)	4 (2)	5 (3)	20 (8)	22 (8)
Native American	69 (7)	41 (7)	116 (8)	2 (1)	3 (2)	1 (<1)	21 (8)	27 (10)
Black	44 (4)	24 (4)	59 (4)	3 (2)	10 (6)	7 (4)	11 (4)	10 (4)
Other	85 (8)	66 (11)	96 (7)	2 (1)	n/a	5 (3)	19 (7)	19 (7)
Ethnicity								
Hispanic	302 (30)	205 (33)	406 (29)	17 (11)	22 (14)	23 (14)	72 (28)	82 (31)
Non-Hispanic	705 (70)	406 (66)	1000 (71)	140 (89)	139 (86)	146 (86)	187 (72)	183 (69)
Not known	1 <1)	1 (<1)	n/a	1 (<1)	n/a	1 (<1)	n/a	n/a
Duration of RA (years)								
mean	9.0	8.7	9.3	11.4	11.0	12.6	6.3	6.4
Rheumatoid Factor								
negative	234 (23)	123 (20)	281 (20)	40 (25)	44 (27)	36 (21)	65 (25)	67 (25)
positive	776 (77)	489 (80)	1125 (80)	118 (75)	117 (73)	134 (79)	194 (75)	198 (75)
Oral corticosteroids								
Yes	455 (45)	244 (40)	629 (45)	91 (58)	94 (58)	88 (52)	122 (47)	128 (48)
No	555 (55)	368 (60)	777 (55)	67 (42)	67 (42)	82 (48)	137 (53)	137 (52)
Number of Previous DMARDs/TNF inhib								
Mean	1.6	1.7	1.6	2.1	2.0	1.9	1.1	1.2

*Pooled DMARD inadequate responders in studies WA17822, WA17823 and WA18063
**Includes MTX
Adapted from Table 21 of Module 2.7.3, Tables 9 and 10 of WA17824 CSR, and Tables 10 and 11 of WA18062 CSR

Table 5 above and Table 6 below summarize the baseline demographics, disease characteristics, and disease activity of the treatment groups within the studies and show that the treatment groups were well balanced with respect to these characteristics.

The majority of patients in the tocilizumab RA pivotal studies were female, Caucasian, and rheumatoid factor (RF) positive, with a mean age in the early fifties. Differences in the target populations between the studies were reflected in disease duration and number of previous DMARDs: WA18062 targeted patients who had a history of active disease despite TNF inhibitor therapy; these patients had longer disease duration and exposure to a higher number of previous DMARDs. WA17824 targeted patients who were MTX-naive; these patients had shorter disease duration and fewer previous DMARDs.

Baseline disease activity parameters were consistent with the targeted population of RA patients with moderately to severely active disease (Table 6).

Table 6 Baseline Disease Activity

Integrated Summary of Baseline Disease Activity (ITT populations/PP population of WA17824)								
	Pooled DMARD Inadequate Responders*			TNF Inadequate Responders (WA18062)			Early RA (WA17824)	
	Placebo + DMARD** n = 1010	TCZ 4mg/kg + DMARD** n = 612	TCZ 8 mg/kg + DMARD** n = 1406	Placebo + MTX n = 158	TCZ 4mg/kg + MTX n = 161	TCZ 8 mg/kg + DMARD** n = 170	MTX n = 259	TCZ 8 mg/kg n = 265
DAS28 (max 10, >5=high) Median	6.7	6.6	6.7	6.8	6.8	6.7	6.8	6.8
Baseline CRP (normal ≤1 mg/dL) Mean	2.4	2.3	2.5	3.7	3.1	2.8	3.0	2.9
Baseline ESR (normal ~15-25 mm/hr) Mean	48.2	47.1	48.1	54.6	51.3	49.1	48.9	49.9
Tender Joint Count (max 68 joints) Mean	29.4	29.8	30.1	30.4	31.3	31.7	31.1	32.2
Swollen Joint Count (max 66 joints) Mean	18.3	18.0	19.0	18.9	19.5	18.9	18.9	19.3
Physician Global (100 mm VAS) Mean	63.3	62.7	63.4	67.5	66.5	66.4	63.2	63.2
Patient Global (100 mm VAS) Mean	64.2	62.6	65.0	70.9	70.4	70.2	65.4	64.0
Patient Pain (100 mm VAS) Mean	57	55.8	57.9	64.1	63.5	64.7	61.3	59.2
HAQ-DI (max 3) Mean	1.5	1.5	1.5	1.7	1.7	1.7	1.5	1.6

*Pooled DMARD inadequate responders in studies WA17822, WA17823, and WA18063
**Includes MTX
Adapted from Table 22 of Module 2.7.3, Table 12 of WA17824 CSR, and Table 13 of WA18062 CSR

6.1.4 Patient Disposition

Table 7 below summarizes the disposition of the patients in the 5 pivotal trials. Overall, a small proportion of patients in each treatment arm discontinued from the studies. In studies WA17822, WA17823, and WA18063, approximately 90% of patients in each treatment arm completed the studies. In studies WA17824 and WA18062, the proportion of placebo patients discontinuing was higher, up to 20%. WA17824 only included a small number of patients in a placebo-controlled substudy; these patients discontinued for a variety reasons other than adverse events. In WA18062, the majority of placebo group patients discontinued for lack of effect. In all 5 studies, a similar proportion of patients discontinued due to adverse events (AE) in the placebo and active treatment arms.

Table 7 Patient Disposition

Summary of Patient Disposition by Trial and Treatment														
RA Population:	DMARD Inadequate			DMARD Inadequate			Early RA			TNF Inadequate			DMARD Inadeq.	
	WA17822			WA17823			WA17824			WA18062			WA18063	
	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo* n (%)	MTX n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 8 n (%)
ITT Population	204	213	205	393	399	398	101	284	288	158	161	170	413	803
Completed	189 (93)	185 (87)	191 (93)	356 (91)	373 (93)	366 (92)	82 (81)	262 (92)	268 (93)	127 (80)	138 (86)	152 (89)	370 (90)	751 (94)
Entered Escape	68 (33)	31 (15)	19 (9)	150 (38)	67 (17)	41 (10)	14 (14)	11 (4)	7 (2)	66 (42)	31 (19)	20 (12)	45 (11)	19 (2)
Total discontinuations	15 (7)	28 (13)	14 (7)	36 (9)	26 (7)	33 (8)	19 (19)	22 (8)	20 (7)	33 (21)	25 (16)	23 (14)	43 (10)	53 (7)
Discontinuation due to AEs	8 (4)	16 (8)	12 (6)	12 (3)	16 (4)	22 (6)	5 (5)	11 (4)	9 (3)	10 (6)	10 (6)	11 (6)	8 (2)	32 (4)
SAEs (other than death)	1	5	4	4	7	3	0	3	2	5	2	3	3	13
Deaths	1	0	0	1	0	0	0	1	3	0	0	0	2	2
Other AE	6	11	8	7	9	19	5	7	4	5	8	8	3	17
Other withdrawals	7 (3)	12 (6)	2 (1)	24 (6)	10 (3)	11 (3)	14 (14)	11 (4)	11 (4)	23 (15)	15 (9)	12 (7)	35 (8)	21 (3)
Insufficient treatment effect	4	3	0	13	2	1	4	3	1	19	6	4	15	3
Protocol violation	1	1	0	2	0	0	2	0	0	0	2	2	3	0
Lost to follow-up	0	1	0	1	1	0	4	1	4	0	4	1	2	2
Patient choice	2	6	1	8	7	9	3	7	6	4	2	4	13	15
Other	0	1	1	1	0	1	1	0	0	0	1	1	2	1
Sources:	Fig 2, Tables 6&7; pg 170-171			Fig 2, Tables 6,7,51; pg 164-165			Fig 3, Tables 6&72 sections 3.1.1 & 7.3			Fig 2, Tables 5&6; pg 192			Fig 2, Table 5 section 3.5.2.4	

*Placebo controlled substudy

6.1.5 Analysis of the Primary Endpoint(s)

The primary endpoint for the studies was the proportion of ACR20 responders at Week 24. As shown in Table 8 below, in each study, a higher proportion of patients achieved ACR20/50/70 responses in the TCZ treatment groups compared with the control groups. Studies WA17822 and WA17823 assessed the effect of TCZ at 4 mg/kg and 8 mg/kg doses compared to placebo add-on therapy in patients who had inadequate response to MTX at 10-25 mg weekly. Study WA18063 investigated the effect of TCZ 8 mg/kg compared to placebo add-on therapy in patients who had inadequate response to a variety of DMARDs, including MTX. Study WA18062 evaluated the effect of TCZ 8 mg/kg and 4 mg/kg compared to placebo add-on therapy in patients who had previously had incomplete response to TNF inhibitor treatment. In each comparison, patients who received TCZ as add-on therapy had a statistically significantly higher rate of response than did patients in the placebo add-on control arms.

Study WA17824 compared TCZ 8 mg/kg monotherapy to methotrexate monotherapy in MTX naïve patients. It was designed as a non-inferiority trial. Patients started on 7.5 mg MTX weekly. At Week 4, if the patient had any swollen or tender joints, the MTX dose was increased to 15 mg. At Week 8, if the patient had any swollen or tender joints, the MTX dose was increased to 20 mg. The pre-specified non-inferiority margin was 12%; that is, non-inferiority would be demonstrated if the lower limit of the 95% confidence interval (CI) of TCZ minus MTX was $\geq$ -0.12. The primary analysis utilized the per-protocol population and is displayed in Table 11 below. The results of an analysis using the intent-to-treat (ITT) population were similar to the primary analysis and are displayed in Table 8. This trial successfully demonstrated the non-inferiority of TCZ compared to MTX. In the event of a demonstration of non-inferiority, the protocol specified a comparison of superiority. The results of this analysis demonstrated that the proportion of ACR20 responders in the TCZ group exceeded the proportion of ACR20 responders in the MTX group, and the difference was statistically significant.

Table 8 Proportion of ACR20/50/70 Responders at Week 24

Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment (ITT Populations)					
Study	**Pbo + DMARD****	**TCZ 4mg/kg + DMARD****	**TCZ 8mg/kg + DMARD****	**p-value (4 mg/kg)**	**p-value (8 mg/kg)**
Patients with incomplete response to MTX or other DMARDs					
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
WA18063	(n=413)		(n=803)		
ACR20	**24**		**61**		**<0.0001**
ACR50	9		38		<0.0001
ACR70	3		20		<0.0001
Patients with incomplete response to prior TNF inhibitor treatment					
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
MTX naive/Early RA patients					
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 for primary analysis population

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 19 of WA17822 CSR, Tables 17 & 18 of WA17823 CSR, Tables 17 & 22 of WA17824 CSR
Tables 21 & 23 of WA18062 CSR, and Tables 17 & 20 of WA18063 CSR

Subgroup Analyses

The treatment effect of TCZ was further explored in analyses of the proportion of ACR20 responders at Week 24 for patients subgrouped by demographic characteristics, geographic region (Table 9), and disease characteristics (Table 10). Patients from studies WA17822, WA17823 and WA18063 were pooled as these characteristics were similar at baseline for the target population of patients who had active disease despite MTX or other DMARD therapy in these studies.

As shown in Table 9 and Table 10 below, treatment with TCZ resulted in a higher proportion of ACR20 responders than did treatment with placebo for all subgroups analyzed. For certain subgroups, for example patients over 75 years of age or patients in the "Other" racial demographic category, the proportion of ACR20 responders in the TCZ 4 mg/kg group exceeded the proportion of responders in the TCZ 8 mg/kg group. However, the small number of patients in these subgroups precludes definitive conclusions.

Table 9 Subgroup Analyses of ACR20 Responders by Demographic Characteristics and Geographic Region

Subgroup Analyses of the Proportion of ACR20 Responders by Demographic Characteristics and Geographic Region, Pooled DMARD Inadequate Responders in Studies WA17822, WA17823, and WA18063 (ITT Population)						
Subgroup	Placebo + DMARD Total n = 1010		TCZ 4 mg/kg + DMARD Total n = 612		TCZ 8 mg/kg + DMARD Total n = 1406	
	category, n	responder, n (%)	category, n	responder, n (%)	category, n	responder, n (%)
Age						
<50 years	390	110 (28)	390	110 (28)	484	**314 (65)**
50-64 years	457	122 (27)	241	115 (48)	685	**385 (56)**
65-75 years	140	25 (18)	92	45 (49)	212	**124 (58)**
>75 years	23	4 (17)	9	**5 (56)**	25	9 (36)
Race						
Native American	69	25 (36)	41	26 (63)	116	**81 (70)**
Asian	88	19 (22)	42	17 (40)	127	**75 (59)**
Black	44	11 (25)	24	10 (42)	59	**29 (49)**
White	724	181 (25)	439	211 (48)	1008	**591 (59)**
Other	85	25 (29)	66	**40 (61)**	96	56 (58)
Gender						
Female	833	215 (26)	511	250 (49)	1154	**686 (59)**
Male	177	46 (26)	101	54 (53)	252	**146 (58)**
Weight						
<60 kg	252	64 (25)	160	88 (55)	345	**223 (65)**
60-100 kg	667	177 (27)	405	205 (51)	951	**555 (58)**
>100 kg	87	18 (21)	43	11 (26)	104	**52 (50)**
BMI						
<18.5	31	9 (29)	16	8 (50)	44	**31 (70)**
18.5-24.9	347	85 (24)	225	125 (56)	496	**310 (62)**
25-29.9	340	94 (28)	198	90 (45)	454	**268 (59)**
≥30	287	71 (25)	167	80 (48)	403	**220 (55)**
Geographic Region						
North America	309	73 (24)	128	53 (41)	489	**234 (48)**
So/Cen America	229	82 (36)	155	89 (57)	318	**220 (69)**
Europe	357	85 (24)	258	126 (49)	438	**283 (65)**
Rest of World	115	21 (18)	71	36 (51)	161	**95 (59)**

Adapted from Tables etsumacr20poolwk241-246 of Module 2.7.3 Summary of Clinical Efficacy

Table 10 Subgroup Analyses of the Proportion of ACR20 Responders by Disease Characteristics

Subgroup Analyses of the Proportion of ACR20 Responders by Disease Characteristics, Pooled DMARD Inadequate Responders in Studies WA17822, WA17823, and WA18063 (ITT Population)						
Subgroup	Placebo + DMARD Total n = 1010		TCZ 4 mg/kg + DMARD Total n = 612		TCZ 8 mg/kg + DMARD Total n = 1406	
	category, n	responder, n (%)	category, n	responder, n (%)	category, n	responder, n (%)
Disease Duration						
≤2 yrs	208	62 (30)	109	64 (59)	274	163 (59)
>2 to ≤5 yrs	201	52 (26)	136	70 (51)	289	179 (62)
>5 to ≤10 yrs	251	61 (24)	157	85 (54)	325	192 (59)
>10 yrs	350	86 (25)	210	85 (40)	517	298 (58)
RF status						
Positive	776	201 (26)	489	253 (52)	1125	687 (61)
Negative	234	60 (26)	123	51 (41)	281	145 (52)
Baseline DAS28						
<Median	529	139 (26)	325	168 (52)	692	404 (58)
≥Median	469	121 (26)	281	134 (48)	703	427 (61)
Baseline CRP (mg/dL)						
<0.3	101	27 (27)	*	*	152	72 (47)
≥0.3 to <1	323	79 (24)	*	*	385	217 (56)
≥1 to <3	328	84 (26)	*	*	471	271 (58)
≥3 to <10	229	64 (28)	*	*	352	240 (68)
≥10	29	7 (24)	*	*	46	32 (70)
Oral Corticosteroids						
Yes	613	175 (29)	392	198 (51)	779	481 (62)
No	397	86 (22)	220	106 (48)	627	351 (56)
Number of Previous DMARDs						
0	262	82 (31)	122	62 (51)	373	220 (59)
1	306	86 (28)	213	118 (55)	407	249 (61)
2	207	51 (25)	142	72 (51)	305	196 (64)
3	119	23 (19)	72	37 (51)	166	93 (56)
≥4	116	19 (16)	63	15 (24)	155	74 (48)

*Analysis not provided
Adapted from Tables 60 and etsumacr20poolwk248-2413 of Module 2.7.3 Summary of Clinical Efficacy

Sensitivity Analyses

The primary analysis for 4 out of the 5 studies (excepting WA17824, which was a non-inferiority comparison) was the comparison of the proportion of ACR20 responders in the TCZ 8 mg/kg + DMARD treatment group vs. the placebo + DMARD group, using the ITT population. Missing data (i.e., due to patient discontinuation or escape, or insufficient ACR core variables to calculate the ACR20) were handled using a nonresponder imputation.

To explore the effect of the specified imputation technique on the study results, sensitivity analyses were conducted using other imputation techniques. The applicant performed a sensitivity analysis utilizing last-observation-carried forward (LOCF) for missing ACR core variables. FDA conducted an additional analysis utilizing baseline-observation-carried forward (BOCF) for missing ACR core variables. Table 11, below, illustrates the difference in outcomes using these different imputation techniques. Results of these sensitivity analyses are consistent with the results of the primary analysis.

The primary analysis for WA17824 was a non-inferiority comparison of TCZ 8 mg/kg monotherapy vs. placebo for the per-protocol population. The per-protocol population included all patients in the ITT population who adhered to the protocol. For the primary method of analysis, no imputation of missing post-baseline values was performed for the physician global, patient global, patient pain VAS, HAQ-DI scores, or acute phase reactants; LOCF was used to derive tender joint counts (TJC) or swollen joint counts (TJC) if missing. As a sensitivity analysis, LOCF was utilized for any missing ACR core variables; results were consistent with the primary analysis. An additional sensitivity analysis was performed utilizing the ITT population with LOCF for missing ACR core variables. Again, results were very similar to results obtained from the primary analysis.

Table 11 Sensitivity Analyses of the Primary Endpoint

Sensitivity Analyses of the Primary Endpoint, Percentage of Patients with ACR20 Response at Week 24					
Study	**Pbo + DMARD****	**TCZ 4mg/kg + DMARD****	**TCZ 8mg/kg + DMARD****	**p-value (4 mg/kg)**	**p-value (8 mg/kg)**
Patients with incomplete response to MTX or other DMARDs, ITT Population					
WA17822	(n=204)	(n=213)	(n=205)		
Primary Analysis	**26**	48	**58**	<0.0001	**<0.0001**
LOCF of ACR Components	27	53	60	<0.0001	<0.0001
BOCF of ACR Components	27	49	59	<0.0001	<0.0001
WA17823	(n=393)	(n=399)	(n=398)		
Primary Analysis	**27**	51	**56**	<0.0001	**<0.0001**
LOCF of ACR Components	29	54	60	<0.0001	<0.0001
BOCF of ACR Components	28	51	57	<0.0001	<0.0001
WA18063	(n=413)		(n=803)		
Primary Analysis	**24**		**61**		**<0.0001**
LOCF of ACR Components	26		64		<0.0001
BOCF of ACR Components	24		61		<0.0001
Patients with incomplete response to prior TNF inhibitor treatment, ITT Population					
WA18062	(n=158)	(n=161)	(n=170)		
Primary Analysis	**10**	30	**50**	<0.0001	**<0.0001**
LOCF of ACR Components	13	35	54	<0.0001	<0.0001
BOCF of ACR Components	11	31	51	0.1005	0.0002
MTX naive/Early RA patients, Non-inferiority Assessment					
Study	**MTX**		**TCZ 8 mg/kg**	**Tx Diff**	**95% CI**
WA17824	PP n = 259		PP n = 265		
	ITT n = 284		ITT n = 286		
Primary Analysis (PP Pop)	**52**		**71**	**0.21**	**(0.13,0.29)***
LOCF (PP Pop)	55		72	0.20	(0.12,0.29)
ITT Analysis	52		70	0.19	(0.11,0.27)

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

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 18 of WA17822 CSR, Tables 17 & p. 677 of WA17823 CSR, Tables 16, 17 and p.757 of WA17824 CSR
Tables 21 & 22 of WA18062 CSR, and Tables 17 & 18 of WA18063 CSR

6.1.6 Secondary endpoint(s)

The applicant pre-specified 36 secondary endpoints for these trials (see 9.4 Individual Study Reports for details) However, to control the rate of false positive conclusions resulting from multiple secondary endpoints, the applicant proposed an

acceptable, prospectively-defined fixed sequence approach for the statistical testing for each individual study. (See the statistical review of the statistical analysis plan for the 5 pivotal studies, November 2, 2006, under IND 11972, and appendix 2 of the statistical review by Dr. Joan Buenconsejo).

Secondary endpoint of ACR50 and ACR70 responders at Week 24

Secondary endpoints for all the studies included the proportion of patients with ACR50 and ACR70 responses at 24 weeks. The results of these analyses are displayed in conjunction with the primary endpoint of ACR20 response in Table 8 of section 6.1.5 above. Although proportionally lower than the percentage of ACR20 responders, the percentage of ACR50 and ACR70 responders was higher in the TCZ 4 mg/kg (where applicable) and TCZ 8 mg/kg treatment groups when compared to the control groups in the 5 studies. These differences were statistically significant, with the exception of ACR70 responders in the TCZ 4 mg/kg group of Study WA18062, which enrolled more refractory patients with history of inadequate response to TNF inhibitors.

Secondary endpoint of mean changes from baseline in individual ACR components

Consistent with the overall results, treatment with TCZ resulted in greater improvement compared to control groups, in all ACR components (Table 12 below), as assessed by mean change from baseline to Week 24. The 95% CI of the difference between the TCZ groups and the control groups excluded zero for all core variables in all studies except WA17824, which was designed as a non-inferiority comparison of TCZ 8 mg/kg monotherapy with optimized MTX monotherapy. In Study WA17824, TCZ 8 mg/kg appeared to effect greater improvement than MTX in all parameters except for patient pain and patient global assessment, where the mean improvement was greater for the TCZ-treated group, but the 95% CI of the difference did not exclude zero.

Table 12 Mean Change in ACR Components, Baseline to Week 24

Summary of Change in ACR Components, baseline to Week 24, by Trial and Treatment													
RA Population:	DMARD Inadequate			DMARD Inadequate			Early RA		TNF Inadequate			DMARD Inadeq.	
	WA17822			WA17823			WA17824		WA18062			WA18063	
	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	MTX n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 8 n (%)
ITT Population (PP for WA17824)	204	213	205	393	399	398	259	265	158	161	170	413	803
SJC (66 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 264	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-4.3	-8.5	-10.5	-2.5	-7.4	-8.5	-7.8	-11.7	-0.5	-6.8	-7.8	-4.9	-10.3
Adjusted Mean Diff.	-	-4.2	-6.2	-	-4.8	-5.9	-	-3.9	-	-6.2	-7.2	-	-5.5
95% CI of Difference	-	(-6.1,-2.3)	(-8.1,-4.2)	-	(-6.1,-3.5)	(-7.2,-4.6)	-	(-5.7,-2.0)	-	(-9.0,-3.5)	(-9.9,-4.5)	-	(-6.7,-4.3)
TJC (68 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 264	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-7.4	-14.5	-17.1	-4.9	-12.1	-14.0	-13.5	-17.1	0.3	-10.5	-14.8	-8.5	-15.7
Adjusted Mean Diff.	-	-7.0	-9.6	-	-7.2	-9.1	-	-3.6	-	-10.8	-15.1	-	-7.1
95% CI of Difference	-	(-10.0,-4.1)	(-12.6,-6.7)	-	(-9.2,-5.2)	(-11.1,-7.1)	-	(-6.3,-1.0)	-	(-14.6,-7.1)	(-18.8,-11.4)	-	(-8.9,-5.4)
Patient Global (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 316	n = 230	n = 242	n = 61	n = 106	n = 129	n = 322	n = 729
Adjusted Mean*	-17.8	-28.8	-32.7	-18.4	-24.9	-25.7	-29.5	-33.5	-15.4	-25.4	-32.8	-16.3	-33.2
Adjusted Mean Diff.	-	-10.9	-14.9	-	-6.5	-7.3	-	-4.1	-	-10.0	-17.4	-	-16.8
95% CI of Difference	-	(-17.1,-4.8)	(-20.9,-8.9)	-	(-11.4,-1.6)	(-12.1,-2.4)	-	(-9.3,+1.2)	-	(-20.3,+0.3)	(-27.8,-7.0)	-	(-20.5,-13.2)
Physician Global (mm)	n = 123	n = 158	n = 173	n = 214	n = 307	n = 320	n = 229	n = 242	n = 61	n = 105	n = 127	n = 322	n = 733
Adjusted Mean*	-32.7	-38.3	-41.6	-28.2	-34.0	-38.3	-31.5	-41.6	-20.0	-30.5	-38.2	-21.6	-35.9
Adjusted Mean Diff.	-	-5.6	-9.0	-	-5.8	-10.1	-	-10.1	-	-10.5	-18.2	-	-14.4
95% CI of Difference	-	(-10.5,-0.8)	(-13.8,-4.2)	-	(-9.6,-1.9)	(-14.0,-6.2)	-	(-14.2,-6.0)	-	(-18.6,-2.5)	(-26.3,-10.0)	-	(-17.3,-11.4)
Patient's Pain (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 317	n = 231	n = 242	n = 61	n = 105	n = 129	n = 322	n = 730
Adjusted Mean*	-14.0	-25.0	-29.8	-13.1	-19.3	-22.2	-29.5	-31.5	-8.6	-21.0	-32.5	-12.8	-29.9
Adjusted Mean Diff.	-	-11.0	-15.8	-	-6.2	-9.1	-	-2.0	-	-12.4	-23.9	-	-17.1
95% CI of Difference	-	(-17.0,-5.0)	(-21.7,-9.9)	-	(-10.9,-1.5)	(-13.9,-4.4)	-	(-7.1,+3.1)	-	(-22.1,-2.6)	(-33.7,-14.1)	-	(-20.8,-13.4)
CRP (mg/dL)	n = 122	n = 157	n = 172	n = 214	n = 308	n = 321	n = 230	n = 242	n = 63	n = 106	n = 129	n = 324	n = 727
Adjusted Mean*	-0.35	-1.66	-2.51	-0.14	-0.70	-1.89	-1.81	-2.85	-0.06	-1.40	-2.58	-0.27	-2.19
Adjusted Mean Diff.	-	-1.30	-2.16	-	-0.57	-1.76	-	-1.04	-	-1.34	-2.52	-	-1.93
95% CI of Difference	-	(-2.01,-0.59)	(-2.86,-1.46)	-	(-1.00,-0.13)	(-2.19,-1.32)	-	(-1.67,-0.41)	-	(-2.54,-0.15)	(-3.72,-1.32)	-	(-2.32,-1.54)
ESR (mm/hr)	n = 122	n = 157	n = 174	n = 211	n = 304	n = 318	n = 229	n = 240	n = 62	n = 107	n = 129	n = 325	n = 732
Adjusted Mean*	-7.1	-25.5	-39.5	-7.1	-19.4	-34.6	-15.1	-37.2	-3.0	-19.7	-37.2	-4.7	-35.6
Adjusted Mean Diff.	-	-18.3	-32.3	-	-12.3	-27.5	-	-22.1	-	-16.7	-34.2	-	-30.9
95% CI of Difference	-	(-24.3,-12.4)	(-38.2,-26.5)	-	(-16.7,-8.0)	(-31.9,-23.2)	-	(-27.2,-17.1)	-	(-25.4,-8.1)	(-43.0,-25.5)	-	(-34.2,-27.6)
HAQ-DI	n = 101	n = 126	n = 141	n = 197	n = 292	n = 301	n = 230	n = 243	n = 62	n = 106	n = 130	n = 322	n = 724
Adjusted Mean*	-0.34	-0.52	-0.55	-0.30	-0.41	-0.50	-0.48	-0.70	-0.05	-0.31	-0.39	-0.20	-0.47
Adjusted Mean Diff.	-	-0.18	-0.21	-	-0.10	-0.19	-	-0.22	-	-0.25	-0.34	-	-0.27
95% CI of Difference	-	(-0.34,-0.02)	(-0.37,-0.05)	-	(-0.20,-0.00)	(-0.30,-0.09)	-	(-0.22,-0.34)	-	(-0.42,-0.09)	(-0.51,-0.17)	-	(-0.34,-0.20)

*ANOVA
LOCF used for tender and swollen joint counts if missing or patient entered escape
No imputation used for missing HAQ score, CRP, ESR, and VAS assessments
Adapted from Tables 23 and 29 of WA17822 CSR, Tables 22 and 27 of WA17823 CSR, Tables 32 and 38 of WA17824 CSR, Tables 33 and 38 of WA18062 CSR, and Tables 25 and 30 of WA18063 CSR

Secondary endpoints related to health-related quality of life (HR-QOL)

The currently published RA Guidance document (ca. 1999) defines a labeling claim of "prevention of disability" (which in recent years has been revised to "improvement in physical function") to recognize the effect of a given treatment on this important patient-reported outcome. Recommended outcome measures to use in support of this claim include the health assessment questionnaire disability index (HAQ-DI), with supportive data from a more general HR-QOL measure such as the Short Form 36 (SF-36), which should not worsen over the course of the trial. The applicant intends to submit longer-term data to support the physical function claim in a separate submission. In the interim, the applicant has submitted data in this submission for secondary endpoints of mean changes from baseline in SF-36 and Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) scale scores at 24 weeks.

The Agency has not historically recognized improvement in fatigue as a distinct claim for RA, as fatigue and inflammation (reflected in the signs and symptoms claim for which ACR response criteria is used as the primary outcome measure) are intertwined, and treatments effective for reducing signs and symptoms would be expected to improve fatigue as well. The FACIT-F is a 13-item scale originally developed to measure fatigue in patients with cancer. Some validation work for this scale in RA patients has been published, however further work on divergent validity and stability of the instrument in RA needs to be performed [Hewlett 2007].

As the SF-36 and FACIT-F endpoints will not be utilized to support labeling claims in this submission, they were not reviewed in detail. However, the applicant's submitted analyses of these endpoints were consistent with the overall conclusion of treatment benefit associated with TCZ treatment.

Exploratory analyses of the proportion of patients achieving clinically meaningful improvements in the HAQ-DI from baseline to Week 24 are discussed below in section 6.1.11 Additional Efficacy Issues/Analyses.

Secondary endpoints related to the DAS28

The DAS28 is a composite index of RA disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and erythrocyte sedimentation rate (ESR) results. An alternative equation is available for use with c-reactive protein (CRP) results. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. Comparing the DAS28 and the ACR response criteria, beyond the differences in number of maximum tender or swollen joints counted, additional variables of physician global assessment, patient pain, and HAQ-DI score are incorporated into the ACR response criteria. The DAS28 has additional utility in measuring the level of disease activity at a given timepoint, whereas the ACR response criteria are calculated as improvement in the variables over a set period of time. A DAS28 score >5.1 is indicative of high disease activity, and <3.2 of low disease activity. The European League Against Rheumatism (EULAR), a counterpart to the American College of Rheumatology (ACR), developed response criteria based on the DAS28 which mirror the ACR response criteria and are based on both the change from baseline in the DAS28 and the numeric value of the DAS28 attained. (See description of calculation in section 9.4 Individual Study Reports, below)

While either of these measures could be reasonably used to assess the effect of an investigational treatment in RA clinical trials, neither measure is clearly superior for this purpose and they are largely redundant. Therefore, for purposes of this efficacy review, the DAS28-based secondary endpoints were not reviewed in detail. However, as per the applicant's report (See Figures 11-13 of Module 2.7.3 Summary of Clinical Efficacy), results for the secondary endpoints of change in DAS28 from baseline to 24 weeks and

the proportion of patients classified as categorical DAS28 responders at 24 weeks were consistent with the primary endpoint results in supporting a favorable effect of treatment with TCZ over control treatment.

The applicant also included a secondary endpoint of the proportion of patients with DAS28 score <2.6 at 24 weeks as a reflection of the ability of TCZ treatment to effect disease remission. At present, proposed definitions of minimal disease activity and remission based on the various disease activity indices are undergoing validation work and discussion in the wider rheumatology community. Definitive conclusions and consensus on the most accurate and clinically useful definitions have not yet been made. The RA Guidance document defines evidence for a labeling claim of remission to include both remission by ACR criteria and radiographic arrest (no radiographic progression by Larsen or modified Sharp method) over a continuous six-month period while off all antirheumatic therapy. A similar achievement requiring ongoing therapy would be given a labeling claim of "complete clinical response." The applicant has not provided sufficient data to support these claims. However, the applicant's analysis of the proportion of patients achieving a DAS28 score of <2.6 at Week 24 demonstrated a statistically significantly higher proportion of patients achieving this score in the TCZ groups compared with the control groups (See Table 42 of Module 2.7.3 Summary of Clinical Efficacy) and is consistent with the overall results in supporting the conclusion of clinical benefit of TCZ treatment.

Secondary endpoint of ACRn

To better describe the range of treatment effect observed across the study population, the applicant utilized a cumulative distribution analysis of ACR response, ACRn, at Week 24. These analyses were confirmed by FDA and are presented below. In each study, patients achieved higher levels of response in the TCZ treatment groups than in the control groups. As shown in Figures 1-5 below, the response profile curves of the TCZ treatment groups clearly separate from the control groups and were higher. Overall response was distinguishably and consistently higher for the TCZ 8 mg/kg group compared to TCZ 4 mg/kg as well, but was not assessed statistically. Although patients in the optimized methotrexate monotherapy group of WA17824 demonstrated a high cumulative response profile, the response profile of patients in the TCZ 8 mg/kg monotherapy group was higher. The differences in the profile curves of the TCZ treatment groups (both 8 mg/kg and 4 mg/kg where applicable) versus the control groups within each study were statistically significant, as tested using Kolmogorov-Smirnov ($p < 0.0001$ for all comparisons; see statistical review by Dr. Joan Buenconsejo).

Time course of ACR response

[redacted] Dr. Buenconsejo confirmed the analyses of proportion of ACR20 and ACR50 responders by week for each study. b(4)

These are displayed in Figures 6-10 below. ACR20 responses increase by Week 2 and generally appear to plateau at Week 12-16. The scale for ACR50 responses in the graphs below ranges from 0 to 50, rather than 0 to 100; the proportions are in fact lower than for ACR20 responses. However, it appears that an increase in ACR50 responses is notable by Week 2-4, with a steady increase in the proportion of responders out to Week 24. The applicant pre-specified generalized estimating equation (GEE) analyses to assess for treatment by visit interactions and provided these in this submission; none were found, indicating that the treatment difference between the TCZ groups and control groups was consistent at each time point.

Percentage improvement in Disease Activity, ACRn, at Week 24
Analyses by Joan Buenconsejo, Ph.D.

X axis = Percentage improvement in disease activity, ACRn, scale 0-100
Y axis = Percent of patients improved, scale 0-100
WA17822, 17823, 18062: Blue line = TCZ 8 mg/kg, Black line = TCZ 4 mg/kg, Red line = Placebo
WA18063: Black line = TCZ 8 mg/kg, Red line = Placebo

Figure 1 Study WA17822

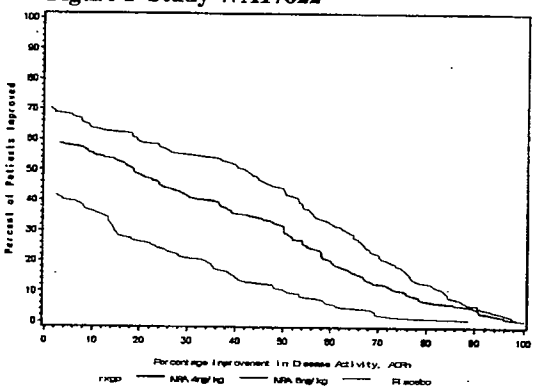


Figure 2 Study WA17823

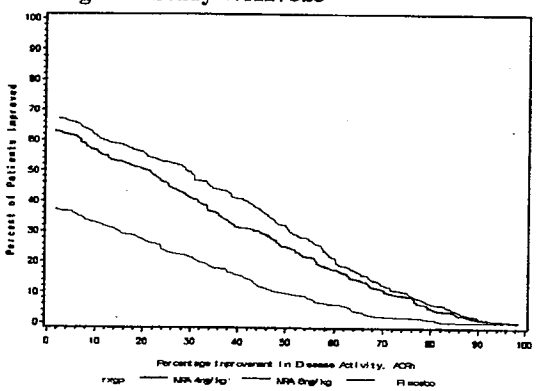


Figure 3 Study WA18062

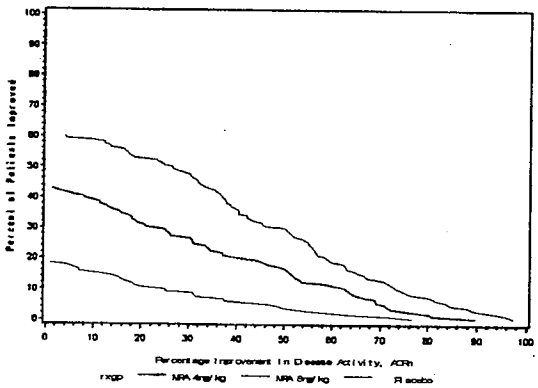
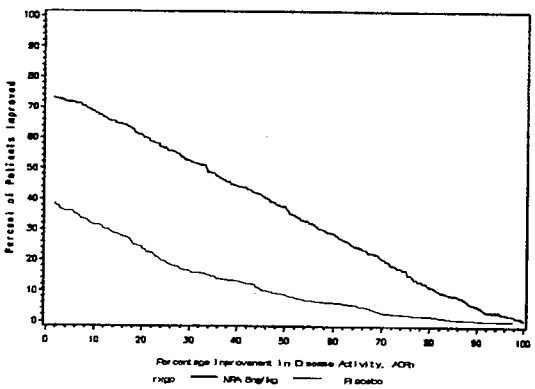
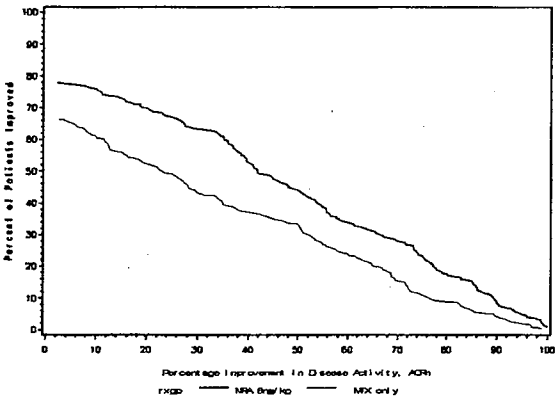


Figure 4 Study WA18063



Percentage improvement in Disease Activity, ACRn, at Week 24 (continued)
X axis = Percentage improvement in disease activity, ACRn, scale 0-100
Y axis = Percent of patients improved, scale 0-100
WA17824: Black line = TCZ 8 mg/kg, Red line = MTX

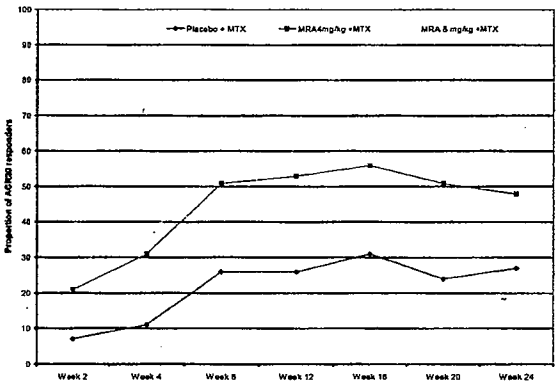
Figure 5 Study WA17824

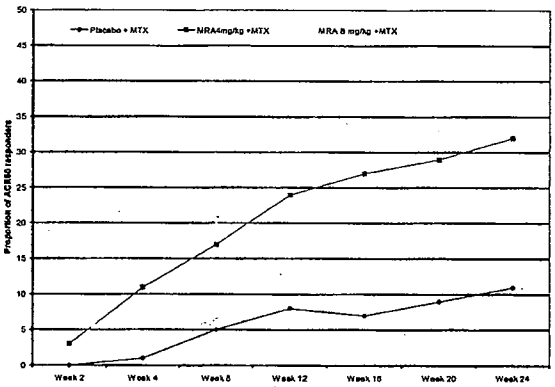


Proportion of ACR Responders by Week
Analyses by Joan Buenconsejo, Ph.D., FDA

Left hand column: ACR 20 responders, scale 0-100
Right hand column: ACR 50 responders, scale 0-50
Yellow line = TCZ 8 mg/kg, Pink line = TCZ 4 mg/kg, Blue line = Placebo

Figure 6: Study WA17822





Proportion of ACR Responders by Week (continued)
Left hand column: ACR 20 responders, scale 0-100
Right hand column: ACR 50 responders, scale 0-50
Pink line = TCZ 8 mg/kg, Blue line = Placebo

Figure 7: Study WA17823

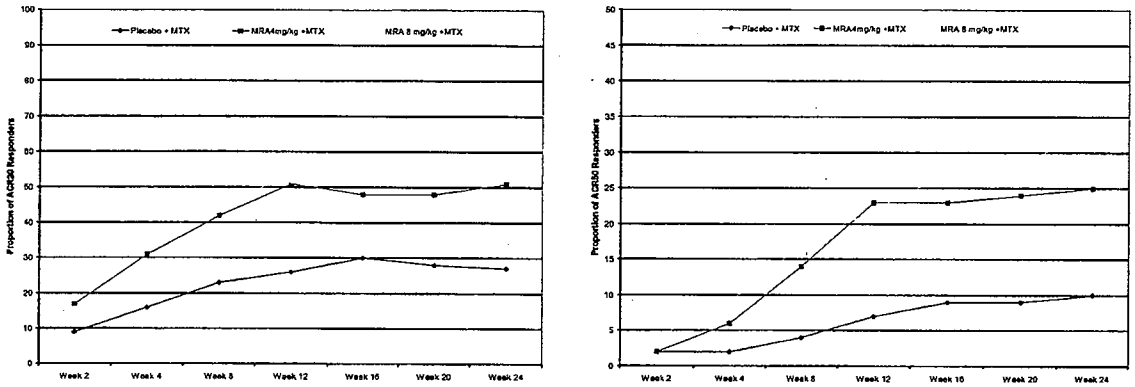


Figure 8: Study WA18062

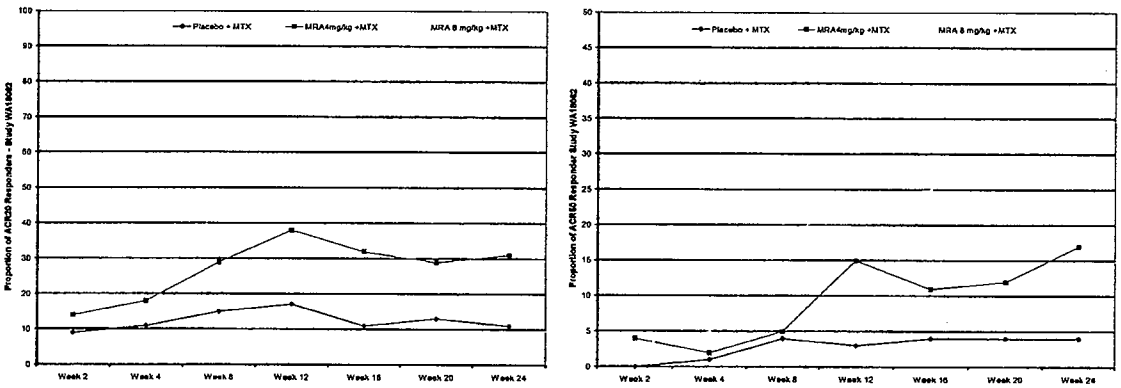
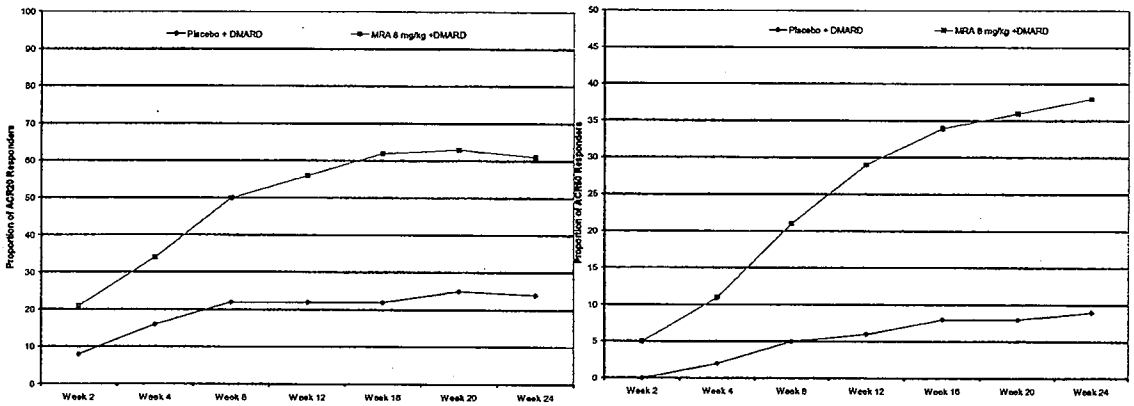
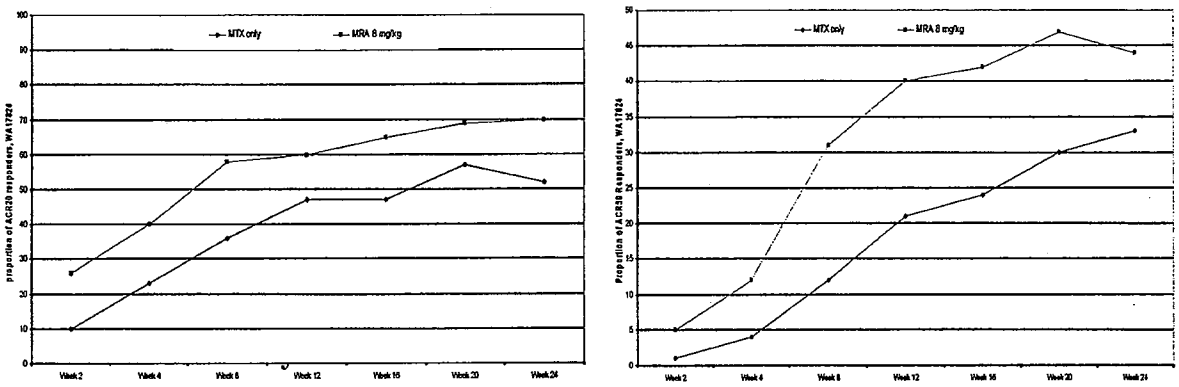


Figure 9: Study WA18063



Proportion of ACR Responders by Week (continued)
Left hand column: ACR 20 responders, scale 0-100
Right hand column: ACR 50 responders, scale 0-50

Figure 10: Study WA17824
Pink line = TCZ 8 mg/kg, Blue line = MTX



6.1.7 Other endpoints

The applicant also pre-specified a secondary endpoint of change from baseline in [redacted] However, in RA, decreased hemoglobin is considered to be a reflection of the bone marrow suppressive effects of chronic inflammation; increased hemoglobin (to a maximum within normal limits) would be expected to result when inflammation is adequately controlled. Therefore, an increase in hemoglobin is not considered to represent a distinct benefit that is not otherwise captured by the primary efficacy claim, but rather an associated laboratory finding of the anti-inflammatory effect of treatment, similar to effects on inflammatory markers such as ESR or CRP. Furthermore, a change in a laboratory parameter, such as hemoglobin, does not in and of itself reflect a clinical benefit. For these reasons, the change in hemoglobin endpoint was not reviewed in detail; however the applicant's described results for hemoglobin (section 3.2.7.1 of Module 2.7.3. Summary of Clinical Efficacy) are consistent with the effect of TCZ on other laboratory parameters that directly reflect inflammation (e.g. ESR/CRP) and support the conclusion that TCZ treatment reduces inflammation in RA.

b(4)

6.1.8 Subpopulations

Refer to subgroup analyses in section 6.1.5.

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

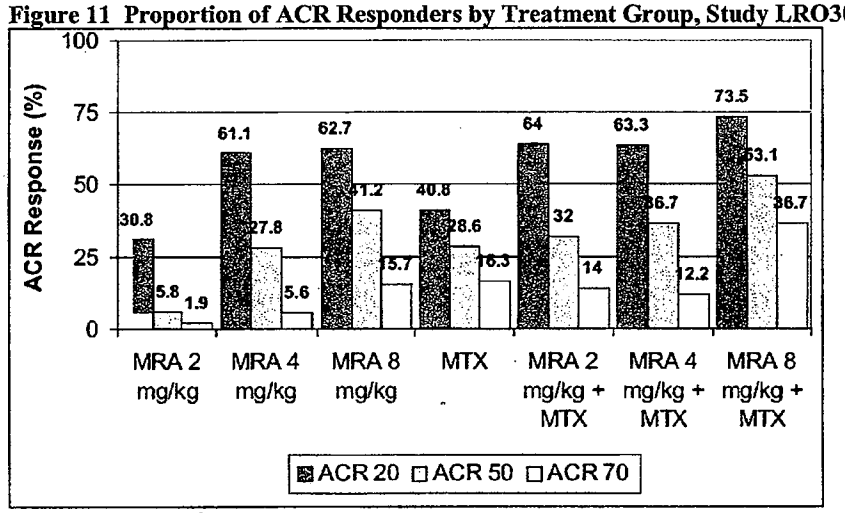
Dose selection for the Phase 3 program was primarily based on the results of Phase 2 Study LRO301, a randomized, double-blind, controlled 20-week study conducted at 57 sites in Europe (354 patients) and applicanted by Chugai Pharmaceuticals. Patients were randomly allocated, stratified by low (10 or 12.5 mg) medium (15 or 17.5 mg) or high (20 to 25 mg) baseline MTX use, to one of seven treatment groups:

1) TCZ 2 mg/kg every 4 weeks + placebo
2) TCZ 2 mg/kg every 4 weeks + MTX
3) TCZ 4 mg/kg every 4 weeks + placebo
4) TCZ 4 mg/kg every 4 weeks + MTX
5) TCZ 8 mg/kg every 4 weeks + placebo
6) TCZ 8 mg/kg every 4 weeks + MTX
7) placebo infusion every 4 weeks + MTX

Patients remained on their baseline MTX dose during the study unless they were randomized to placebo MTX.

Results for the full analysis population at Week 16, using LOCF for missing core variables, are described in Figure 11, below (Figure C from the LRO301 CSR). Based on differing efficacy in the TCZ 2 mg/kg + placebo group compared to the rest of the treatment groups, and lack of apparent safety benefit in favor of the 2 mg/kg dosing, the applicant elected to proceed with the 4 mg/kg and 8 mg/kg doses in the pivotal trials.

Figure 11 Proportion of ACR Responders by Treatment Group, Study LRO301



Source: Figure C from LRO301 CSR

Studies WA17822, WA17823, and WA18062 contained 4 mg/kg and 8 mg/kg dose groups. Efficacy and safety results are displayed by treatment group in this review to facilitate dose-response exploration between these two doses. Overall these results suggest a dose-response relationship for most efficacy and safety parameters; treatment with the 8 mg/kg dose appears to have increased efficacy over the 4 mg/kg dose, however it is also associated with higher rates of serious infection and other AEs.

The applicant provided analyses evaluating the effect of weight-based dosing (8 mg/kg) vs. fixed dosing (560 mg) on the pharmacokinetic parameters of AUC, Cmax, and Cmin (see figure 12, below). These analyses suggest that weight-based dosing does not necessarily result in similar AUC across the weight range, as heavier patients had higher AUC. However, with fixed-dose, the heaviest patients did have lower AUC than other patients and the lightest patients had higher AUC. FDA pharmacometrician Dr. Atul Bhattaram evaluated the effect of body weight on ACR20 response rates and proportion of patients experiencing AEs (Figures 13 and 14, below). Despite somewhat higher AUC, heavier patients tended to have lower ACR20 response rates. The proportion of patients experiencing AEs also increased with increasing body weight, however a similar increase was noted in the placebo-treated group, making it difficult to ascribe this increase to higher TCZ exposures.

Figure 12 Effect of weight based vs. fixed dose regimen on pharmacokinetic parameters

After 8 mg/kg dose | After 560 mg fixed dose

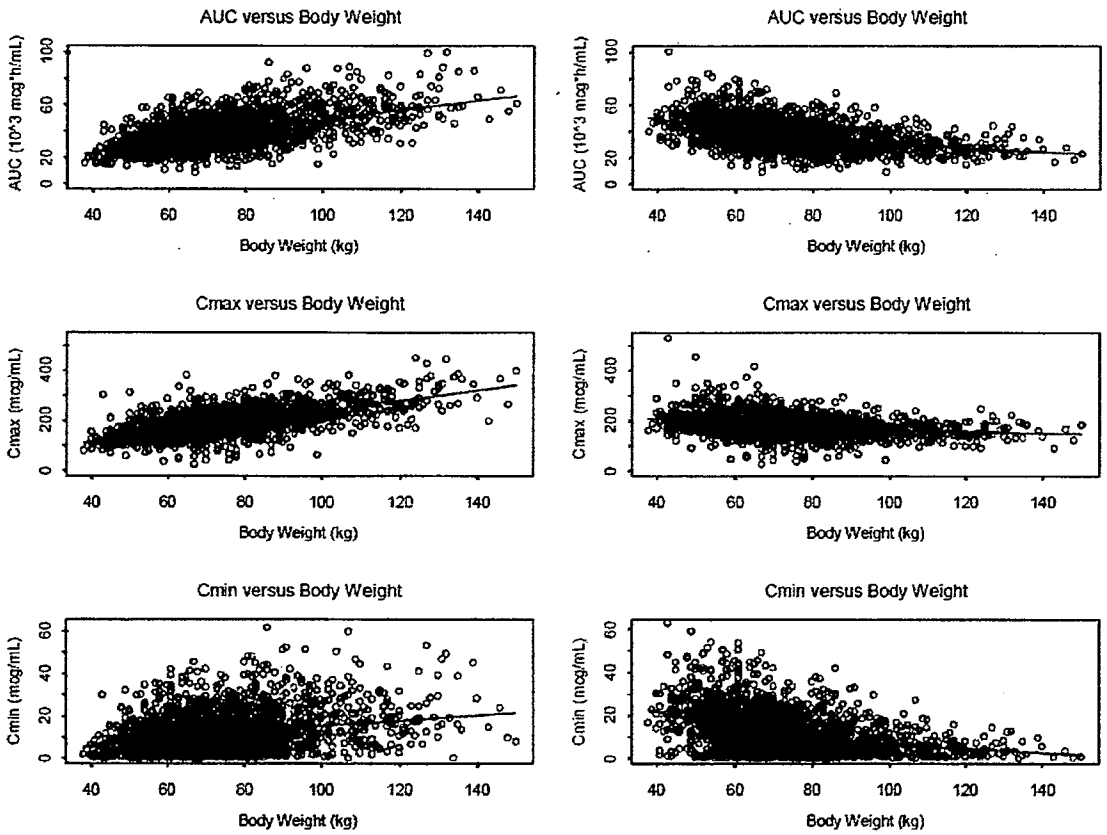


Figure 13 ACR20 Response Rates are Lower with Increasing Body Weight

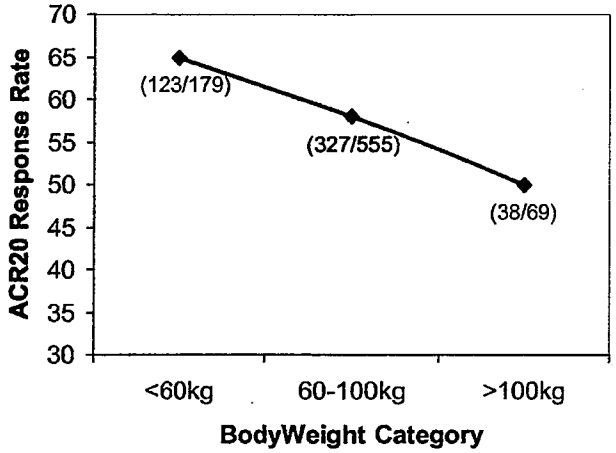
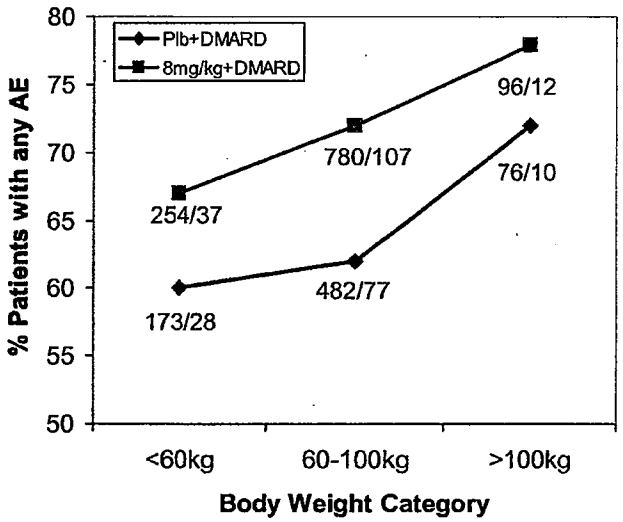


Figure 14 Increasing Proportion of AEs with Body Weight



6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

As noted in section 6.1.6 Secondary endpoint(s), the time course of ACR20 and ACR50 responses support the conclusion that TCZ treatment was effective throughout the 24-week controlled-period. Maximal ACR20 responses were achieved by Week 12-16 and continued at the same level to Week 24. The proportion of ACR50 responders increased at each timepoint up to Week 24, but remained lower than the proportion of ACR20 responders.

Table 13 Proportion of ACR Responders in the Long-Term Extensions

Proportion of ACR Responders Over Time in the Long-Term Extensions									
	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120
Total withdrawn due to insufficient therapeutic response	6	12	22		20		10		2
Originating Study									
WA17824, n	**508**	**450**	**391**	**273**	**175**	**92**	**32**	**5**	**0**
ACR20 responders (%)	318 (63)	312 (69)	293 (75)	207 (76)	137 (78)	75 (82)	28 (88)	5 (100)	
ACR50 responders (%)	200 (39)	207 (46)	216 (55)	145 (53)	102 (58)	58 (63)	20 (62)	4 (80)	
ACR70 responders (%)	111 (22)	127 (28)	140 (36)	97 (36)	62 (35)	39 (42)	15 (47)	2 (40)	
WA18062, n	**388**	**357**	**327**	**260**	**192**	**120**	**53**	**16**	**0**
ACR20 responders (%)	214 (55)	223 (62)	210 (64)	173 (67)	135 (70)	79 (66)	35 (66)	12 (75)	
ACR50 responders (%)	112 (29)	132 (37)	119 (36)	115 (44)	91 (47)	52 (43)	19 (36)	8 (50)	
ACR70 responders (%)	40 (10)	61 (17)	57 (17)	58 (22)	51 (27)	32 (27)	11 (21)	3 (19)	
Pooled DMARD inadequate, n	**1530**	**1419**	**1324**	**1202**	**993**	**719**	**451**	**260**	**63**
ACR20 responders (%)	923 (60)	902 (64)	937 (71)	867 (72)	763 (77)	563 (78)	368 (82)	221 (85)	48 (76)
ACR50 responders (%)	564 (37)	557 (39)	629 (48)	582 (48)	529 (53)	395 (55)	268 (59)	168 (65)	39 (62)
ACR70 responders (%)	269 (18)	285 (20)	349 (26)	331 (28)	323 (33)	249 (35)	162 (36)	100 (38)	21 (33)

Source: Table etacr20507090i_4msu and Stex_itr_i of 120 day safety update

Table 13 above summarizes the proportion of ACR 20/50/70 responders at 12 week intervals in the long-term extensions through October 1, 2007. The number of patients withdrawing due to insufficient therapeutic response remained low during the extensions, ranging from 1-2% of the existing population at a given time interval. The proportion of patients meeting ACR20/50/70 response criteria remained as high as at the 24-Week timepoint at all successive time points in the long-term extension to date. Although response rates appeared to increase, definitive conclusions cannot be drawn from these data, which are open-label and do not account for drop-outs. However, overall these data support the conclusion that tocilizumab treatment remains effective over time.

6.1.11 Additional Efficacy Issues/Analyses

Clinically relevant improvements in HAQ-DI

As mentioned above in section 6.1.6, the Agency recognizes a distinct claim in RA for "improvement in physical function" based on outcome measures such as the HAQ-DI. This instrument assesses a patient's level of functional ability and includes questions pertaining to fine movements of the upper extremity, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients respond on a four-level difficulty scale ranging from zero (no difficulty) to three (unable to do). The eight category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to 3 (completely disabled). The most widely accepted figure on the minimal clinically important difference in the HAQ-DI score is an improvement (decrease) of 0.22 units. Therefore, to better assess how many patients achieve a clinically meaningful level of improvement, the Agency has requested responder analyses evaluating the proportion of patients in each treatment group who achieve this level of improvement or higher.

The applicant submitted analyses of the proportion of patients achieving several levels of HAQ-DI improvement; however, HAQ data are missing for a significant proportion of patients in the studies. Table 14 below summarizes the proportion of patients achieving clinically significant levels of improvement in the HAQ-DI for patients with HAQ data at baseline and Week 24. The proportion of patients achieving meaningful improvement in HAQ-DI was higher in the TCZ groups compared to the control groups. However, the amount of missing data was highest in the control groups; this imbalance raises the possibility of bias.

Table 14 Proportion of Patients with Clinically Meaningful Improvements in HAQ-DI

Proportion of Patients with Clinically Significant Levels of HAQ-DI Improvement (ITT populations/PP population of WA17824)								
	Pooled DMARD Inadequate Responders*			TNF Inadequate Responders			Early RA (WA17824)	
	Placebo + DMARD** n = 1010	TCZ 4mg/kg + MTX n = 612	TCZ 8 mg/kg + DMARD** n = 1406	Placebo + MTX n = 158	TCZ 4mg/kg + MTX n = 161	TCZ 8 mg/kg + MTX n = 170	MTX n = 259	TCZ 8 mg/kg n = 265
Missing data	390 (39)	194 (32)	240 (17)	96 (60)	55 (34)	40 (24)	29 (11)	22 (8)
Pts with baseline and Week 24 results	620	418	1166	62	106	130	230	243
≥ 0.25 u decrease	319 (51)	288 (69)	792 (68)	20 (32)	56 (53)	86 (66)	156 (68)	187 (77)
p value (vs control grp)		0.0003	<0.0001					
≥ 0.3 u decrease	250 (40)	244 (58)	698 (60)	15 (24)	44 (42)	72 (55)	136 (59)	174 (72)
p value (vs control grp)		0.0033	<0.0001					
≥ 0.5 u decrease	192 (31)	207 (50)	599 (51)	5 (8)	31 (29)	58 (45)	119 (52)	151 (62)
p value (vs control grp)		0.0019	<0.0001					

*Pooled DMARD inadequate responders in studies WA17822, WA17823, and WA18063
**Includes MTX
No imputation for missing data; Cochran-Mantel-Haenszel used to calculate p-values
Sources: Tables 46, 47, and etsumhaqimppoolwk24l from Module 2.7.3 Summary of Clinical Efficacy

To explore further, FDA statistician Dr. Joan Buenconsejo performed additional analyses of the HAQ-DI as shown in Table 15 below. These analyses were not performed by the applicant and no multiplicity adjustments were made. In these analyses, a responder is defined as patients who had at least 0.22 unit decreased in HAQ-DI score from baseline at the end of week 24. Missing data were imputed using LOCF and BOCF, with the proportion of responders being based on the total number of patients in each treatment group having at least baseline HAQ results. The proportion of patients having missing baseline HAQ data was similar among the various treatment groups of each study. These analyses support the conclusion that TCZ treatment provides a treatment benefit with respect to improvement in HAQ-DI when compared to the control groups.

Table 15 FDA Responder Analysis of HAQ-DI at Week 24 (ITT)

Study		Placebo	TCZ4mg/kg	TCZ8mg/kg	MTX
WA17822§	Total	**N=204**	**N=213**	**N=205**	
	Baseline HAQ (N)	n=169	n=177	n=170	
	LOCF	72 (43%)	109 (62%) *	109 (64%) *	
	BOCF	58 (34%)	92 (52%) *	95 (56%) *	
WA17823§	Total	**N=392**	**N=399**	**N=399**	
	Baseline HAQ (N)	n=368	n=376	n=375	
	LOCF	153 (42%)	229 (61%) *	235 (63%) *	
	BOCF	112 (30%)	201 (53%) *	209 (56%) *	
WA17824†	Total			**N=286**	**N=284**
	Baseline HAQ (N)			n=285	n=283
	LOCF			213 (75%) **	188 (66%)
	BOCF			201 (71%) **	174 (61%)
WA18062§	Total	**N=160**	**N=163**	**N=175**	
	Baseline HAQ (N)	n=157	n=159	n=170	
	LOCF	34 (22%)	73 (46%) *	100 (59%) *	
	BOCF	21 (13%)	58 (36%) *	86 (51%) *	
WA18063‡	Total	**N=415**		**N=804**	
	Baseline HAQ (N)	n= 411		n= 794	
	LOCF	180 (44%)		526 (66%) *	
	BOCF	155 (38%)		499 (63%) *	

† Monotherapy
§ +MTX
‡ +DMARDs
* p<0.001 (unadjusted)
** p<0.01 (unadjusted)
Source: Table 22 of the statistical review by Dr. Joan Buenconsejo

7. INTEGRATED REVIEW OF SAFETY

Summary of Safety Results and Conclusions

Four of the five pivotal RA studies were 24-week studies (WA17822, WA17824, WA18062, WA18063). Upon completing the 24-week controlled period, patients could continue open-label treatment with TCZ 8 mg/kg in long-term extension studies for up to 5 years. Study WA17823 is designed as a 2-year study (1st year double-blind, 2nd year open-label); 6-month interim data were submitted with this BLA. Six-month safety data from all 5 studies were pooled for an integrated analysis of safety by treatment groups. Almost 3800 patients have been exposed to TCZ in the Roche RA program, including placebo-treated patients who entered escape or open-label treatment. Over half of these patients have been exposed for up to 1 year, and almost 1500 have been exposed for up to 18 months. The majority of TCZ exposure has been to the higher dose of 8 mg/kg. Supportive safety data from trials conducted by Roche's co-development partner Chugai Pharmaceuticals were also reviewed. The amount of safety data provided far exceeds minimum ICH E1 standards and is consistent with the safety databases required of approved immunosuppressive therapeutic biologics for RA.

Four primary safety concerns arising from the data submitted in this BLA are as follows:

1) Serious infections:
During the 6-month controlled period, patients receiving TCZ 8 mg/kg + DMARD had the highest exposure-adjusted incidence of serious infections, approximately 5.7 serious infections per 100 patient-years exposure compared to 3.9 serious infections per 100 patient-years exposure in the placebo control group. Patients receiving TCZ 4 mg/kg + MTX also had a higher incidence of serious infections compared to placebo (4.7 serious infections per 100 patient-years), but the incidence was comparatively lower than with the TCZ 8 mg/kg combination therapy group. Patients on TCZ 8 mg/kg monotherapy did not have an elevated incidence of serious infections (3.2 serious infections per 100 patient-years). TCZ treatment was not associated with reactivation of latent tuberculosis (TB) infection during the clinical trials despite the lack of protocol mandated TB screening or prophylaxis and the world-wide distribution of study sites.

2) Laboratory abnormalities:
TCZ, when combined with DMARDs, was associated with an increased incidence of laboratory abnormalities, such as decreased white blood cell count (WBC) and platelets, elevations in lipid parameters, and most significantly, liver enzyme elevation. Changes in these parameters were temporally associated with TCZ treatment and resolved once treatment discontinued. Changes in WBC and platelets generally remained within the normal range. Increases in lipid parameters were on average small, but affected all parameters and total cholesterol/HDL ratio increased. Most liver enzyme abnormalities were transient and less than 3 times the upper limit of normal. Five percent of patients in the TCZ 8 mg/kg and 4 mg/kg combination therapy groups experienced at least one ALT elevation between 3 and 5 x ULN, compared to 4% of patients on MTX monotherapy and 1% of patients on placebo+ DMARD. The pattern of liver enzyme elevations was very similar in the methotrexate and TCZ 8 mg/kg monotherapy treatment arms of study 17824, where both monotherapy arms showed fewer instances of liver enzyme elevation compared to the tocilizumab combination treatment groups. However, TCZ 8 mg/kg monotherapy was associated with a higher rate of total bilirubin elevation to up to 3x ULN.

A single case meeting Hy's Law criteria (transaminase elevations >3 x ULN + bilirubin elevation > 2 x ULN without evidence of biliary obstruction) was identified in the TCZ global safety database and occurred on open-label TCZ 8 mg/kg with initiation of MTX after the patient completed 6-months of TCZ monotherapy without significant changes in transaminases. Abnormalities resolved with discontinuation of MTX and TCZ. Overall, in patients experiencing liver enzyme elevations who continued on study, modification of treatment regimen (a reduction of the dose of DMARD, an interruption of TCZ infusion and/or reduction of TCZ dose from 8 mg/kg to 4 mg/kg) led to a decrease or normalization without subsequent elevation of liver enzymes or occurrence of hepatobiliary AEs. Currently available data on over 3700 patients treated with TCZ for up to 2 years contain no clinical events of hepatitis or hepatic failure.

3) Malignancies:
Malignancies occurred at similar rates in the TCZ groups as in the placebo group during the 6-month controlled period. These rates ranged from 1.5 to 1.6 malignancies per 100 patient-years and were slightly higher than published background rates in RA patients (1.3-1.4 per 100 patient-years). Based on interim data submitted from the long-term extension studies, malignancy rates have not risen over the extended duration of exposure in these trials.

4) Uncommon but serious adverse events such as GI perforations and demyelinating adverse events:
During the 6-month controlled period, 3 gastrointestinal (GI) perforation events occurred in the TCZ 8 mg/kg treatment groups compared to none in the placebo or TCZ 4 mg/kg per treatment groups. Overall, GI perforations were uncommon, a total of 16 events occurred in the TCZ global RA program through data cut-off, which includes approximately 4700 patients and over 7900 patient-years of exposure. Four cases of demyelinating adverse events were also observed in the global RA program.

Overall, the safety data from the Roche pivotal trials and long-term extensions, and the global experience with TCZ depict the profile of an immunosuppressant, with its inherent risks, such as serious infections. TCZ manifested effects on laboratory parameters, such as decreased white blood cell count, increases in lipids, and most significantly, liver enzyme elevation, although these were not associated with clinical adverse events in the controlled setting of the clinical trial experience. Malignancies, GI perforations, and demyelinating adverse events were observed in the clinical trials, however the relative risk and role of TCZ treatment in the development of these adverse events is not well defined. These types of potential risks are not unique in the RA therapeutic armamentarium and have historically been handled via appropriate labeling, which should also be adequate in this case. The clinical trial experience has been extensive, but may not capture the full extent of safety concerns that may arise with long-term IL-6 inhibition.

7.1 Methods

Discussion of Clinical Studies Used to Evaluate Safety

This submission contained 24 week safety data from 5 pivotal trials (Table 4, above), including 6-month interim data from WA17823, which is designed as a 2-year study. These studies were of sufficiently similar design to allow for pooled analyses of the 6-month controlled data, by treatment group.

Long term safety information from RA patients treated with open-label TCZ 8 mg/kg was also provided in this summary. The data are derived from two open-label extension

studies, WA18695 and WA18696, which are ongoing. The clinical cut-off date for the provision of data from the extension study program was April 20th, 2007.

Additional safety information was provided for adverse events of interest from studies in the Chugai clinical development program in RA and other indications up to a clinical cut-off date of August 31st, 2007.

The 120-day safety update includes data from the two long-term extension studies WA18695 and WA18696 (clinical cut-off date of October 1, 2007). Deaths and SAEs occurring through January 31, 2008 are also reported from the ongoing Japanese development program ———————— , spontaneous reports from the treatment of multicentric Castleman's Disease (approved in Japan), compassionate use of TCZ in children with systemic juvenile idiopathic arthritis (SJIA), the ongoing study WA17823, and the ongoing extension studies WA18695 and WA18696. b(4)

7.1.2 Adequacy of Data

Overall, the safety coding and safety datasets and tabulations were adequate to enable review. Verbatim terms were mapped to MedDRA terms and coding dictionaries provided.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The 5 pivotal studies forming the basis of this submission were of sufficiently similar design to enable pooling by treatment arms in that they included a controlled period of 24 weeks, with a stable dosing regimen throughout.

7.2 Adequacy of Safety Assessments

The pooled safety database from the 5 pivotal RA studies provided for a large pre-market clinical experience, comprised of approximately 2600 patients in the 6-month safety population and the long-term extensions; patients and duration of exposure continues to accrue in the long-term extensions, in which patients will be followed for up to 5 years on treatment. The submitted data far exceed minimum ICH (E1) guidelines.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As shown in Table 16 below, almost 3800 patients have been exposed to TCZ in the Roche RA program, including placebo-treated patients who entered escape or open-label treatment. Over half of these patients have been exposed for up to 1 year, and almost 1500 have been exposed for up to 18 months. An additional 1600 patients have been

exposed to TCZ in the supportive studies (data not shown). The majority of TCZ exposure has been to the higher dose of 8 mg/kg.

Table 16 Exposure to Tocilizumab

Exposure in the Roche Tocilizumab RA Pivotal Studies and Long-Term Extensions		
Population	Number of patients	Duration TCZ exposure (patient-yrs)
6 mo safety population, all TCZ	2644	1131
Pooled Long Term Extensions	2562	3685
All Exposure	3778	4142
≤ 3 months	*3474*	*799*
≤ 6 months	*3183*	*1464*
≤ 12 months	*2121*	*1951*
≤ 18 months	*1463*	*2019*
≤ 24 months	*640*	*1178*
≤ 30 months	*113*	*260*
Total exposure, TCZ 4 mg/kg	1181	435
Total exposure, TCZ 8 mg/kg	3242	3707

Source: Table 3 and 4 of 120 day safety update, data cut-off Oct. 1, 2007

7.2.2 Explorations for Dose Response

Refer to section 6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations and section 7.5.1 Dose Dependency for Adverse Findings.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was considered necessary to further explore the safety profile of tocilizumab, which is primarily based on human clinical data.

7.2.4 Routine Clinical Testing

The type and frequency of routine clinical testing of patients in the 5 pivotal studies and long term extensions was adequate. For details, see section 9.4 Individual Study Reports.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Tocilizumab, if approved, would be the first IL-6 inhibitor in class. However, the safety data submitted were evaluated in the context of what is known regarding the safety profile of approved biologic agents for RA, to include TNF inhibitors, rituximab, anakinra, and abatacept. Therefore the data were scrutinized with special attention to serious infections and malignancies. However IL-6 inhibition may pose unique risks, such as neutropenia, elevated liver enzymes and elevated lipid parameters. These potential concerns are also addressed below.

7.3 Major Safety Results and Discussion

Safety overview

The majority of patients in the TCZ RA pivotal studies experienced at least one adverse event (AE) during the course of the trial. The proportion of patients experiencing an adverse event in the TCZ treatment arms was similar to the proportion of patients experiencing an adverse event with MTX monotherapy, and was higher than with placebo.

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. Exposure-adjusted incidence of deaths and serious adverse events (SAE) are discussed in further detail in the next section.

The proportion of patients experiencing an AE leading to withdrawal was small (<5%) in each treatment group but was lowest with placebo. During the double-blind controlled portion of the studies, dose modification entailed temporary withholding of a scheduled dose, e.g., for the first occurrence of AST/ALT elevation >3 X ULN, or for non-serious infections. Background DMARD therapy doses could be modified for toxicity and WA17824 specified scenarios for MTX modification in the protocol. Dose reduction from TCZ 8 mg/kg to TCZ 4 mg/kg was allowed in the long-term extensions for safety reasons, such as AST/ALT elevation or decreased WBC (see Table 32 and Table 33, below).

Table 17 Overview of AEs and Deaths

Overview of AEs and Deaths 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	2562
Pts with any AEs	733 (63)	220 (77)	547 (71)	1134 (72)	230 (80)	1911 (72)	2259 (88)
Deaths	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)
Pts with SAEs	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Pts with AEs leading to withdrawal	28 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Pts with AEs leading to dose modif.	84 (7)	63 (22)	103 (13)	194 (12)	56 (19)	353 (13)	884 (34)

*Includes MTX
Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population
Adapted from Table 15 of Module 2.7.4 and Table 5 of 120 day safety update

Exposure adjusted incidence of deaths, SAEs, SIEs, and malignancies

In the placebo-controlled portions of the trials, patients could escape at Week 16 if they had an inadequate response. In general, a higher proportion of patients in the placebo treatment groups entered escape (see Table 7, above). Thus the overall exposure time of patients to placebo was shorter than the designated 6 months. Conversely, the majority of patients in the long-term safety population have been exposed to TCZ treatment for at least 1 year (see Table 16, above). To account for these differences in exposure for comparison by treatment arms, exposure adjusted incidence rates were calculated for deaths, SAEs, serious infectious events (SIE), and malignancies, summarized in Table 18, below.

Table 18 Exposure Adjusted Incidence of Deaths, SAEs, SIEs, and Malignancies

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	2562
Total patient-years exposure	462	123	321	685	126	1131	3685
Deaths, n (%)	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)
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)	60 (2.3)
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6
No. with ≥1 SAE, n (%)	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Number of SAE	74	15	51	115	12	178	489
SAEs per 100 pt-yrs	16	12	16	17	10	16	13
No. with ≥1 SIE, n (%)	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)
Number of SIE	18	2	15	39	4	58	141
SIEs per 100 pt-yrs	3.9	1.6	4.7	5.7	3.2	5.1	3.8

* Includes MTX
Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population
Adapted from Tables 12, 13, 24, 27 and 38 of Module 2.7.4 Summary of Clinical Safety and source tables STae_py_mal and STrate_ae_s; and tables 4, 5, 9, 20 and stae11_sl of 120 d safety update; p.5 of Amendment 14

Overall, the exposure-adjusted incidence rates of death were not elevated in the TCZ treatment groups compared to the placebo or MTX monotherapy treatment groups, with the exception of the TCZ 8 mg/kg monotherapy treatment group (1% or 2.4/100 pt-yrs compared to 0.3% or 0.9/100 pt-years with placebo). This finding is difficult to interpret because of the small number of deaths involved, namely 3 among 288 patients receiving TCZ 8 mg/kg monotherapy. In addition, if TCZ 8 mg/kg were truly associated with a higher risk of death, it is surprising that TCZ 8 mg/kg in combination with DMARDs does not also show a higher rate of death. Finally, to provide perspective for the death rate in the TCZ 8 mg/kg monotherapy group, we compared the rate to that seen in published studies of mortality in patients with RA. These analyses showed that the exposure-adjusted rate of 2.4 deaths per 100 patient-years in this group is similar to that expected in the RA population based on published mortality rates. For example, in the Olmsted County RA cohort, death rates for female and male RA patients between 1965 and 2005 were relatively constant at 2.4 and 2.5 deaths per 100 person-years, respectively [Gonzalez 2007].

The exposure-adjusted incidence rate of malignancies, including non-melanoma skin cancers, was similar in all treatment groups at 1.5 to 1.6 malignancies per 100 patient-years, with the exception of a slightly higher rate of 2.4 malignancies per 100 patient-years observed in the MTX monotherapy group. If non-melanoma skin cancers are excluded, TCZ treatment group malignancy rates range from 0.8 to 1.2 (long-term safety population) malignancies per 100-patient-years, compared to 0.9 for the placebo-treatment group. These rates are comparable to published malignancy rates from RA patient cohorts:

- National Data Bank for Rheumatic Diseases [Wolfe/Michaud, 2007], 1 non-cutaneous malignancy per 100 patient-years;
- Danish Cancer Registry [Mellemkjaer 1996], 1.3 malignancies per 100 patient-years;
- British Society for Rheumatology Biologics Register (BSRBR), 0.8 to 1.4 malignancies per 100 patient-years

When segmented by age groups and compared to the NCI Surveillance Epidemiology and End Results (SEER) general population database (Table 19, below), RA patients in the Roche Tocilizumab program had a higher incidence of malignancy than would be expected in the U.S. general population. As a caveat, it should be noted that of the total study population in the 5 pivotal studies, 2/3 were from outside the U.S. These data are consistent with published literature stating an increased rate of non-melanoma skin cancers in RA patients on other biologic immunosuppressive therapies. The relative risk of lung cancer for RA patients is not clear, although lung cancer is the one of the most common cancers in the general population (2nd most frequently diagnosed in both Caucasian men and women, 1988-1992, SEER). The relative risk of lymphoma is higher in RA patients, however thus far, only a single case of lymphoma has occurred with TCZ treatment in Roche RA program (See Table 22, below). Overall, the pattern and

frequency of malignancies observed in the TCZ RA program to date appears consistent with what might be expected in RA patients and does not clearly implicate an additional risk attributable to TCZ treatment.

Table 19 Malignancy Rates Compared to SEER, Segmented by Age Groups

Malignancy Incidence Rates in Roche Tocilizumab RA Program, Excluding Non-Melanoma Skin Cancers, Compared to SEER Database General Population and Segmented by Age Groups									
	Combined			Female			Male		
	No. reported	Observed rate per 100 pt-yr	SEER rate per 100 pt-yr	No. reported	Observed rate per 100 pt-yr	SEER rate per 100 pt-yr	No. reported	Observed rate per 100 pt-yr	SEER rate per 100 pt-yr
Total	42	1.02		30			12		
30-34 year olds									
All sites	1	0.593	0.081	1	0.701	0.101	-	-	0.062
Lung	1	0.593	0.001	1	0.701	0.001	-	-	0.001
35-39 year olds									
All sites	-	-	0.125	-	-	0.162	-	-	0.089
40-44 year olds									
All sites	1	0.254	0.207	1	0.298	0.268	-	-	0.146
45-49 year olds									
All sites	2	0.372	0.342	2	0.468	0.410	-	-	0.272
Cervix Uteri	-	-	-	1	0.234	0.015	-	-	-
Breast	-	-	-	1	0.234	0.187	-	-	-
50-54 year olds									
All sites	3	0.438	0.551	2	0.350	0.571	1	0.882	0.530
Cervix Uteri	-	-	-	1	0.175	0.014	-	-	-
Ovary	-	-	-	1	0.175	0.022	-	-	-
Prostate	-	-	-	-	-	-	1	0.882	0.138
55-59 year olds									
All sites	11	1.535	0.876	5	0.856	0.800	6	4.515	0.956
Corpus Uteri	-	-	-	2	0.342	0.067	-	-	-
Breast	-	-	-	2	0.342	0.308	-	-	-
Lung	4	0.557	0.107	-	-	0.092	4	3.006	0.123
Prostate	-	-	-	-	-	-	1	0.749	0.335
Stomach	2	0.278	0.012	1	0.171	0.008	1	0.748	0.017
60-64 year olds									
All sites	9	1.775	1.291	8	2.056	1.062	1	0.848	1.542
Cervix Uteri	-	-	-	1	0.256	0.015	-	-	-
Breast	-	-	-	1	0.256	0.364	-	-	-
Lung	4	0.786	0.191	3	0.768	0.158	1	0.848	0.226
NHL	1	0.196	0.063	1	0.256	0.055	-	-	0.073
65-69 year olds									
All sites	7	1.951	1.796	6	2.200	1.372	1	1.162	2.289
Cervix Uteri	-	-	-	1	0.365	0.015	-	-	-
Colon/Rectal	1	0.278	0.185	1	0.365	0.152	-	-	0.224
Lung	2	0.555	0.291	2	0.730	0.238	-	-	0.352
70-74 year olds									
All sites	7	4.059	2.170	5	3.539	1.624	2	6.415	2.856
Colon/Rectal	1	0.572	0.246	1	0.703	0.202	-	-	0.301
Lung	1	0.572	0.382	1	0.702	0.305	-	-	0.479
Stomach	1	0.572	0.038	1	0.703	0.025	-	-	0.055
75-79 year olds									
All sites	1	1.228	2.453	-	-	1.883	1	9.378	3.266
Colon/Rectal	1	1.228	0.316	-	-	0.273	1	9.378	0.379

18 non-melanoma skin cancers excluded, as they are not collected by SEER; 4135 person-years
All sites number includes malignancies of gammopathy, glioblastoma, metastatic neoplasm, metastatic squamous cell carcinoma and thyroid neoplasm
Data cut-off October 1, 2007; adapted from Table 2, BLA 125276 amendment 14

A similar incidence of serious adverse events was noted in the TCZ treatment groups compared to placebo. TCZ and MTX monotherapy groups had the lowest exposure-adjusted incidence (10 and 12 events per 100 patient-years, respectively). The rate of serious adverse events did not increase with increasing duration of TCZ exposure observed in the long-term safety population.

The incidence rate of serious infections was highest in the TCZ 8 mg/kg + DMARD combination treatment group at 5.7 SIEs per 100 patient-years, and was slightly lower in the TCZ 4 mg/kg + DMARD group at 4.7 SIEs per 100 patient-years. Both rates exceeded the observed rate of 3.9 events per 100 patient-years in the placebo + DMARD group. TCZ and MTX monotherapy groups again had the lowest exposure-adjusted incidence with 3.2 and 1.6 SIEs per 100 patient-years, respectively. The rate of SIEs did not increase with increasing duration of TCZ exposure in the long-term safety population (3.8 SIE per 100 pt-years). Rates of serious infections in RA patients taking TNF inhibitors have been published as approximating 5-6 SIEs per 100 patient-years, compared to 2-4 SIE per 100 patient-years in RA patients taking non-biologic DMARDs [Listing 2005, Dixon 2007].

7.3.1 Deaths

During the TCZ RA pivotal studies and long-term extensions to date, five patients died of cardiac etiologies (4 myocardial infarctions and 1 cardiac failure) and four patients died of infectious etiologies while on TCZ treatment. A line listing of deaths in the Roche TCZ pivotal studies and long term extensions may be found in Table 20, below. Other deaths in the TCZ global program are described in

Table 21. Overall, the numbers and causes of deaths in the program appear to be consistent with what might be expected for the underlying patient population.

Table 20 Line Listing of Deaths in the Roche RA Pivotal Studies

Line Listing of Deaths in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment				
Tx Grp/Pt no.	Age/sex	Last tx day	Day of death	Cause of death
Placebo + DMARD (n = 1170)				
3298	46/M	84	101	Coronary artery thrombosis
5633	55/F	1	103	Wegener's Granulomatosis
7737	55/F	113	140	Pneumonia
6937	68/F	85	135	Intestinal obstruction
MTX (n = 284)				
4141	71/M	119	177	Lung neoplasm malignant
TCZ 8mg/kg + DMARD (n = 1582)				
7722	48/F	113	120	Hemorrhagic stroke, aneurysm rupture
6713	75/F	27	54	Post procedural complication
TCZ 8 mg/kg (n = 288)				
4013	46/F	142	150	Ischemic necrosis of AV node
4221	76/F	29	37	GI hemorrhage
4929	50/F	36	40	Myocardial ischemia
Pooled TCZ long-term extensions (n = 2562)				
3440	73/F	452	534	Gastric cancer
3739	71/F	169	183	Acute myocardial infarction
7328	72/F	229	393	Bacterial bronchitis
6554	63/M	30	47	Suicide
6981	58/F	338	420	Septic shock
8888	75/F	251	268	Pneumonia
5421	59/F	218	472	Diverticular perforation
5423	63/F	225	234	Beta hemolytic strep infection
5883	67/M	336	341	Myocardial infarction
5326	68/F	112	203	Progressive idiopathic polyneuropathy
5151	83/F	78	100	Unknown
3070	70/F	255	357	Metastatic colon cancer
6288	70/M	414	441	Acute renal failure
7366	45/F	473	477	Suicide
5687	57/F	351	372	Myocardial infarction
4943	70/F	169	200	Cardiac failure

Adapted from Table 20 of Module 2.7.4 and Table 6 of 120 day safety update (cut-off date October 1, 2007)

Data beyond 6 months from Study WA17823 were not included in the original submission, as these patients remain on blinded treatment in the study and they are not included in the long-term extensions. An additional 9 deaths were reported through January 31, 2008: 1 metastatic lung cancer, 1 subarachnoid hemorrhage, 1 sepsis, 1 infectious gastroenteritis, 1 staphylococcal sepsis, 2 deaths due to pulmonary embolism, 1 cardiomyopathy, and 1 death from gastroesophageal cancer. The database has not yet been locked for this study, so the treatment assignments for these patients remain unknown.

Table 21 Line Listing of Deaths in the Global Safety Database

Line Listing of Deaths in Tocilizumab-Treated Patients in the Global Safety Database			
Indication	Study	Age/Gender	Cause of death
RA	LRO300	70/F	Myocardial ischemia
	LRO301	61/M	Lung cancer
	MRA009JP	60/F	EBV reactivation/Hodgkin's lymphoma
	MRA214JP	52/M	Gastric cancer/pneumonia
	MRA214JP	81/M	Bronchopulmonary aspergillosis
Systemic JIA	Compassionate	5/F	Acute myeloid leukemia
	Compassionate	4/F	Juvenile arthritis
	MRA324JP	4F	Macrophage activation syndrome
	MRA324JP	22/M	Cardiac amyloidosis
Multiple Myeloma	LRO310	57/F	Pneumonia/cholecystitis/neuro symptoms
	LRO310	67/F	Sepsis
	LRO310	77/F	Multiple myeloma
	LRO310	65/F	Multiple myeloma
	LRO310	71/F	Acute renal failure
	Compassionate	53/M	Multiple myeloma
Castleman's Disease	MRA006JP	66/M	Chronic myelomonocytic leukemia
	ML19367	77/F	Cholestatic jaundice
	ML19367	74/F	Gastrointestinal hemorrhage
	ML19367	72/M	Gastric cancer
	ML19367	34/M	Cerebral hemorrhage
	ML19367	46/M	Acute renal failure
	ML19367	38/F	Respiratory failure/Castleman's disease

Data cut-off April 20, 2007
Adapted from Tables 21 and 22 of Module 2.7.4

5 additional deaths were reported between September 1, 2007 and January 2008 in the Chugai development program. These include two events of respiratory failure, 1 cerebral infarction, 1 pneumonia, and 1 cardiac failure.

7.3.2 Nonfatal Serious Adverse Events

Neoplasms and Malignancy

As discussed above, the overall exposure-adjusted incidence of malignancy in the TCZ RA studies appears to be within the range of what might be expected in the RA patient population. The types of malignancies observed are described in Table 22, below. Few malignancies were observed during the 6-month controlled period of the RA pivotal studies. During the long-term extensions, a total of 65 neoplasms or malignancies were diagnosed; basal cell skin carcinomas occurred most commonly, followed by lung neoplasms and lung cancers.

Table 22 Neoplasms and Malignancies

Neoplasms and Malignancies in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Type and Trial Treatment							
	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	2562
Total patients with ≥1 AE	7 (0.6)	3 (1.1)	5 (0.6)	10 (0.6)	2 (0.7)	17 (0.6)	65 (2.5)
Total neoplasms and malignancies	7	3	6	10	2	18	65
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6
Solid Tumors							
Lung neoplasm	1	-	1	2	-	3	9
Lung cancer	-	1	1	-	-	1	7
Small cell, stage unsp.	-	-	-	-	-	-	2
Adenocarcinoma	-	-	-	-	-	-	2
Squamous cell	-	-	-	-	-	-	1
Non-small cell	-	-	-	-	-	-	1
Not specified	-	1	1	-	-	1	1
Thyroid neoplasm	-	-	-	1	-	1	6
Breast cancer, including in situ	1	-	-	-	-	-	4
Squamous cell carcinoma, unsp	-	-	-	1	-	1	3
Cervical cancer	-	-	1	-	-	1	3
Gastric cancer	-	-	-	-	1	1	2
Prostate cancer	1	-	-	-	-	-	2
Colon or rectal cancer	1	1	-	1	-	1	2
Colon neoplasm	-	-	-	-	-	-	1
Adrenal neoplasm	-	-	-	-	-	-	1
Endometrial neoplasm	-	-	-	-	-	-	1
Glioblastoma	-	-	-	-	-	-	1
Meningeal neoplasm	-	-	-	1	-	1	1
Metastatic neoplasm	-	-	-	-	-	-	1
Ovarian cancer	-	-	-	-	-	-	1
Uterine cancer	-	-	-	1	-	1	1
Hepatic neoplasm	-	-	1	-	-	1	-
Non-melanoma skin CA							
Basal cell carcinoma	1	-	-	1	1	2	12
Bowen's disease	-	-	1	1	-	2	3
Neoplasm, skin	-	-	-	-	-	-	1
Carcinoma in situ, skin	-	-	-	-	-	-	1
Dysplastic nevus syndrome	1	-	-	-	-	-	-
Squamous cell CA, skin	1	-	-	1	-	1	-
Skin cancer, NOS	-	-	1	-	-	1	-
Hematologic/Lymphatic							
Diffuse large B-cell lymphoma	-	-	-	-	-	-	1
Gammopathy	-	-	-	-	-	-	1
T cell lymphoma	-	1	-	-	-	-	-

* Includes MTX
Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population
Adapted from source table STae11_mal of Module 2.7.4 Summary of Clinical Safety, Table 20 of 120 d safety update

Serious Infections

TCZ treatment was associated with a higher risk of serious infections. The numbers and types of serious infections are shown in Table 23, below. Of these, pneumonia and cellulitis were by far the most commonly occurring serious infections. In addition to commonly occurring bacterial infections, treatment with TCZ was associated with an increased incidence of herpes zoster, including herpes zoster ophthalmicus. No other viral reactivation events were noted in the Roche RA program, however a single case of

serious EBV reactivation complicated by non-Hodgkin's lymphoma and resulting in death was observed in the Chugai RA trials. Patients with a history of recurrent infections, including hepatitis B, hepatitis C, and herpes zoster were excluded from the RA trials.

Patients were also excluded from the studies if they had a history of or known active mycobacterial infections, but were not specifically required to have TB screening or prophylaxis; in fact, 68 patients (52 in the TCZ treatment groups) had a history of TB or positive PPD prior to study start. Despite this and the global nature of the studies, only two cases of TB have been diagnosed in the program thus far, and occurred in the long-term extensions: one case of mycobacterial urinary tract infection in a patient who did not have a history of TB risk factors or exposure, and one case of mycobacterial/staphylococcal septic arthritis in a patient who was PPD negative. Additionally, two opportunistic infections were diagnosed: one case of pneumocystis jiroveci pneumonia and one case of mycobacterium avium intracellulare pneumonia.

Thus far, the overall safety profile of TCZ with respect to infections is consistent with that of other immunosuppressants and implicates an increased risk of serious infection with TCZ treatment.

Table 23 Serious Infectious Events

Serious Infectious Events (SIE) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment	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	2562
Total patients with ≥ 1 SIE	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)
Total number of SIEs	18	2	15	39	4	58	141
SIEs per 100 pt-years	3.9	1.6	4.7	5.7	3.2	5.1	3.8
Infections-pathogen unspecified							
Total patients with at least one AE	**17 (2)**	**2 (1)**	**12 (2)**	**18 (1)**	**4 (1)**	**34 (1)**	**90 (4)**
Pneumonia	4	1	5	9	2	16	35
Pneumonia, empyema or necrotizing	-	-	1	1	-	2	1
Abscess	4	-	-	2	-	2	9
Intra-abdominal	1	-	-	1	-	1	2
Soft-tissue	2	-	-	-	-	-	5
Oral	1	-	-	-	-	-	1
Peri-anal	-	-	-	1	-	1	1
Gastroenteritis/Diarrhea	-	-	3	-	-	3	8
Respiratory tract infection	1	-	2	2	-	4	7
Diverticulitis	-	-	-	-	-	-	6
Urinary tract infection	5	-	1	3	-	4	5
Pyelonephritis	1	-	-	2	-	2	2
Sepsis	1	1	2	1	-	3	4
Pulmonary sepsis	-	-	-	-	-	-	1
Urosepsis	1	-	-	-	-	-	1
Skin/soft tissue/nail	-	-	-	-	-	-	4
Osteomyelitis	2	-	1	-	-	1	3
Sinusitis	-	-	-	-	1	1	2
Appendicitis	-	-	-	-	-	-	2
Arthritis/tenosynovitis, infective	-	-	-	-	-	-	2
Wound/post-procedural infection	-	-	-	-	-	-	2
Cholecystitis, acute	-	-	-	-	-	-	1
Otitis media or externa	-	-	-	1	-	1	1
Gingival infection	-	-	-	-	-	-	1
Intervertebral disclitis	-	-	-	-	-	-	1
Meningitis, aseptic	-	-	-	-	-	-	1
Mediastinitis	-	-	-	1	-	1	-
Sialoadenitis	-	-	-	-	1	1	-
Bacterial Infectious Disorders							
Total patients with at least one AE	**1 (<1)**	**0**	**0**	**15 (1)**	**0**	**15 (1)**	**34 (1)**
Cellulitis	1	-	-	11	-	11	21
Cellulitis, gangrenous	-	-	-	-	-	-	1
Staphylococcal cellulitis	-	-	-	1	-	1	-
Erysipelas	-	-	-	1	-	1	2
Bacterial arthritis	-	-	-	2	-	2	3
Staph septic arthritis	-	-	-	1	-	1	-
Enterococcal endocarditis	-	-	-	1	-	1	-
Pneumococcal pneumonia	-	-	-	1	-	1	2
Beta hemolytic strep	-	-	-	-	-	-	1
Bacterial bronchitis	-	-	-	-	-	-	1
C. Difficile colitis	-	-	-	-	-	-	1
Helicobacter gastritis	-	-	-	-	-	-	1
Salmonellosis	-	-	-	-	-	-	1
E. Coli UTI	-	-	-	-	-	-	1
Streptococcal infection NOS	-	-	-	-	-	-	1
Staphylococcal infection NOS	-	-	-	-	-	-	1
Viral Infectious Disorders							
Total patients with at least one AE	**0**	**0**	**0**	**5 (<1)**	**0**	**5 (<1)**	**11 (<1)**
Herpes zoster	-	-	-	4	-	4	7
Herpes zoster ophthalmic	-	-	-	1	-	1	1
Influenza	-	-	-	-	-	-	1
Varicella	-	-	-	-	-	-	1
Viral infection NOS	-	-	-	-	-	-	1
Opportunistic/Mycobact. Infections							
Total patients with at least one AE	**0**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**2 (<1)**
Pneumocystis Jiroveci pneumonia	-	-	1	-	-	1	-
Tuberculosis	-	-	-	-	-	-	1
Mycobacterium Avium pneumonia	-	-	-	-	-	-	1

* Includes MTX

Data cut-off April 20, 2007; October 1, 2007 for long-term safety population

Adapted from Table 27 of Module 2.7.4 Summary of Clinical Safety and Table 9 of 120 d safety update

Serious Adverse Events

The numbers and types of SAE are displayed in Table 24, below. Serious infections were the most common type of serious adverse event, followed by the gastrointestinal (GI) disorder and injury system-organ classes (SOC). The injury SOC was primarily populated by events of falls and fractures. GI events included GI perforations, which are discussed in greater detail below.

The overall rate of myocardial infarctions (MI) in the RA Phase 3 studies and long term extensions remained consistent over time (data not shown). As of the final data cut-off for the 120-day safety update (January 31, 2008 for deaths and SAE), 15 MI were diagnosed in approximately 4158 patient-years exposure for a rate of 0.35 per 100 patient-years. This rate is not elevated compared to published rates of MI in RA patients, which range from 0.47 per 100 patient-years in the ARAMIS database to 0.76 per 100 patient-years in the National Data Bank for Rheumatic Diseases.

Similarly, the rate of cerebrovascular accident events in patients treated with TCZ during the Phase 3 studies is not elevated compared to published rates. Nine CVA were diagnosed in 4158 patient-years exposure for a rate of 0.22 per 100 patient years. Note that Table 16 does not list two of the events: two patients who remain on blinded treatment in WA17823 (designed as a 2 year study). Published rates range from 0.11 per 100 patient-years in female RA patients within the Nurse's Health Study to 0.76 per 100 patient-years in the UK General Practice Research database.

Table 24 Serious Adverse Events

Serious Adverse Events (SAE) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions (>1 Occurrence in Tocilizumab Group***) by Trial Treatment	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	2562
Total patients with ≥ 1 SAE	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Total number of SAEs	74	15	51	115	12	178	489
SAEs per 100 pt-yrs	16	12	16	17	10	16	13
Infections and Infestations**	**17 (1)**	**2 (1)**	**13 (2)**	**38 (2)**	**4 (1)**	**55 (2)**	**133 (5)**
Gastrointestinal Disorders	**6 (<1)**	**1 (<1)**	**3 (<1)**	**14 (1)**	**2 (1)**	**19 (1)**	**44 (2)**
Abdominal pain	-	-	-	1	-	1	6
Diverticular/Other GI perforation	-	-	-	2	1	3	4
Gastritis/erosive gastritis	-	-	-	1	-	1	3
Inguinal hernia	-	-	-	-	-	-	3
Diarrhea	1	-	-	1	-	1	2
Esophagitis	-	-	1	1	-	2	2
Ischemic colitis/intestinal ischemia	-	-	-	-	-	-	2
Gastric ulcer	-	-	-	1	1	2	1
Pancreatitis	-	-	-	1	-	1	2
Vomiting	1	-	-	1	-	1	2
Injury, Poison., Procedural Complic.***	**4 (<1)**	**3 (1)**	**4 (<1)**	**14 (1)**	**1 (<1)**	**19 (1)**	**50 (2)**
Neoplasms, benign/malignant/NOS**	**4 (<1)**	**3 (1)**	**3 (<1)**	**2 (<1)**	**1 (<1)**	**6 (<1)**	**38 (1)**
Musculoskeletal/Connective Tissue***	**9 (1)**	**1 (<1)**	**3 (<1)**	**5 (<1)**	**0**	**8 (<1)**	**29 (1)**
Cardiac Disorders	**5 (<1)**	**0**	**1 (<1)**	**7 (<1)**	**2 (1)**	**10 (<1)**	**22 (1)**
Atrial fibrillation	-	-	-	1	-	1	5
Myocardial infarction/AMI	2	-	1	-	-	1	5
Angina/acute coronary synd.	1	-	-	2	-	-	5
Coronary artery disease	-	-	-	2	-	2	2
Arrhythmia	-	-	-	1	-	1	2
Congestive heart failure/LV dysfxn	-	-	-	1	-	1	3
Nervous System Disorders	**3 (<1)**	**0**	**6 (1)**	**9 (1)**	**1 (<1)**	**16 (1)**	**17 (1)**
Sciatica	-	-	-	1	-	1	4
Cerebrovascular accident	-	-	-	2	-	2	3
Carotid artery stenosis	-	-	1	1	-	2	2
Hemorrhagic stroke	-	-	-	2	-	2	-
Syncope	-	-	2	-	-	2	1
Respiratory/Thoracic/Mediastinal	**3 (<1)**	**1 (<1)**	**2 (<1)**	**4 (<1)**	**0**	**6 (<1)**	**15 (1)**
Interstitial lung disease/IPF	-	-	2	1	-	3	3
Pulmonary embolism	1	1	-	3	-	3	3
COPD	-	-	-	-	-	-	2
Rheumatoid Lung	-	-	-	-	-	-	2
Vascular Disorders	**4 (<1)**	**1 (<1)**	**2 (<1)**	**2 (<1)**	**0**	**4 (<1)**	**15 (1)**
Hypertension	-	-	-	1	-	1	3
Deep vein thrombosis	2	-	1	-	-	1	2
Peripheral vascular disorder	-	-	-	-	-	-	2
Renal/Urinary	**1 (<1)**	**0**	**1 (<1)**	**3 (<1)**	**0**	**4 (<1)**	**8 (<1)**
Nephrolithiasis/ureterolithiasis	-	-	-	2	-	2	6
Hepatobiliary	**1 (<1)**	**0**	**0**	**2 (<1)**	**1 (<1)**	**3 (<1)**	**6 (<1)**
Cholelithiasis	1	-	-	1	-	1	2
General and Admin site	**4 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**0**	**2 (<1)**	**6 (<1)**
Non-cardiac chest pain	2	-	-	-	-	-	2
Reproductive/Breast	**1 (<1)**	**0**	**1 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**6 (<1)**
Uterine hemorrhage	-	-	-	1	-	1	2
Blood and Lymphatic	**2 (<1)**	**0**	**4 (<1)**	**2 (<1)**	**0**	**6 (<1)**	**4 (<1)**
Leukopenia/neutropenia	-	-	2	2	-	4	4
Psychiatric Disorders	**1 (<1)**	**1 (<1)**	**2 (<1)**	**1 (<1)**	**-**	**3 (<1)**	**4 (<1)**
Skin and Subcutaneous	**1 (<1)**	**0**	**0**	**2 (<1)**	**0**	**2 (<1)**	**2 (<1)**
Immune System	**0**	**0**	**2 (<1)**	**0**	**0**	**2 (<1)**	**-**
Anaphylactic reaction	-	-	2	-	-	2	-
Metabolism/Nutrition	**2 (<1)**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**-**
Surgical/Medical Procedures	**0**	**0**	**1 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**-**
Abortion, induced	-	-	1	1	-	2	-
Ear and Labyrinth	**2 (<1)**	**0**	**0**	**0**	**0**	**0**	**2 (<1)**
Endocrine	**0**	**0**	**0**	**1 (<1)**	**0**	**1 (<1)**	**1 (<1)**
Investigations	**0**	**0**	**0**	**1 (<1)**	**0**	**1 (<1)**	**-**

* Includes MTX
Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population
** See separate SIE and Neoplasms tables for details
***Preferred terms not listed for Injury and Musculoskeletal SOCs
Adapted from Table 24 of Module 2.7.4 Summary of Clinical Safety and Table stae11_sl of 120 d safety update

7.3.3 Dropouts and/or Discontinuations

The study protocols mandated discontinuation for patients meeting certain laboratory criteria, such as AST/ALT $\geq$ 3 X ULN that persisted or recurred upon re-exposure of treatment, AST/ALT > 5 X ULN, total bilirubin >2.5 mg/dl or unconjugated bilirubin > 2 X ULN, and ANC < 0.5 x 10^9/L. As summarized in Table 25 below, these protocol-mandated laboratory discontinuations were the most common reason for discontinuation. Laboratory abnormalities are discussed in further detail below. Infections and malignancies were the next most common types of events causing discontinuation.

Table 25 Adverse Events Causing Discontinuation

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, Part 1 of 3	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	2562
Total patients discontinuing due to AE	28 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Total number of AEs causing discont.	29	15	38	75	11	124	159
Investigations							
Total patients with at least one AE	**3 (<1)**	**4 (1)**	**15 (2)**	**37 (2)**	**2 (1)**	**54 (2)**	**40 (2)**
ALT or AST increased[a]	2	4	10	21	1	32	22
Neutrophils decreased[b]	-	-	3	6	1	10	8
Bilirubin increased[c]	-	-	2	7	-	9	4
Platelet count decreased[d]	-	-	-	1	-	1	2
Triglycerides increased	-	-	-	-	-	-	2
Platelet count increased	-	-	-	-	-	-	1
Weight increased	-	-	-	-	-	-	1
Eosinophilia	-	-	-	1	-	1	-
PPD positive	-	-	-	1	-	1	-
Hemoglobin decreased	1	-	-	-	-	-	-
Infections and Infestations							
Total patients with at least one AE	**7 (1)**	**1 (<1)**	**5 (1)**	**8 (<1)**	**1 (<1)**	**14 (<1)**	**24 (1)**
Pneumonia	2	-	2	1	1	4	7
Empyema	-	-	-	1	-	1	1
Cellulitis	-	-	-	2	-	2	3
Diverticulitis	-	-	-	-	-	-	2
Respiratory tract infection	-	1	1	-	-	1	2
Appendicitis	-	-	-	-	-	-	1
Intra-abdominal abscess	-	-	-	1	-	1	1
Sepsis, pulmonary	1	-	-	1	-	1	1
Osteomyelitis	1	-	1	-	-	1	1
Dermatitis infection	-	-	-	1	-	1	-
Septic arthritis	-	-	-	1	-	1	-
Pyelonephritis, acute	-	-	-	1	-	1	-
Pneumocystis jiroveci	-	-	1	-	-	1	-
Mycobacterium Avium Intracellulare	-	-	-	-	-	-	1
Tuberculosis	-	-	-	-	-	-	1
Nasopharyngitis	-	-	-	-	-	-	1
Varicella	-	-	-	-	-	-	1
Urinary tract infection	1	-	-	-	-	-	1
Wound infection	-	-	-	-	-	-	1
Post-procedural infection	1	-	-	-	-	-	-
Purulent discharge	1	-	-	-	-	-	-
Neoplasms, benign/malig/NOS							
Total patients with at least one AE	**1 (<1)**	**3 (1)**	**1 (<1)**	**0**	**1 (<1)**	**2 (<1)**	**27 (1)**
Lung cancer[e]	-	1	-	-	-	-	7
Breast cancer	-	-	-	-	-	-	3
Gastric cancer	-	-	-	-	1	1	2
Colon cancer	-	1	-	-	-	-	2
Prostate cancer	1	-	-	-	-	-	2
Cervical cancer	-	-	1	-	-	1	1
Colon neoplasm	-	-	-	-	-	-	1
Diffuse large B-cell lymphoma	-	-	-	-	-	-	1
Glioblastoma	-	-	-	-	-	-	1
Lymphoproliferative disorder	-	-	-	-	-	-	1
Meningioma	-	-	-	-	-	-	1
Metastatic neoplasm	-	-	-	-	-	-	1
Metastatic squamous cell carcinoma	-	-	-	-	-	-	1
Ovarian cancer	-	-	-	-	-	-	1
Squamous cell carcinoma							1
Uterine cancer	-	-	-	-	-	-	1
T cell lymphoma	-	1	-	-	-	-	-

* Includes MTX
Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population
Multiple occurrences of the same AE in one individual are counted only once
Events on escape therapy are excluded
a) includes preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, liver function test abnormal
b) includes Blood and Lymphatic System Disorders preferred terms of neutropenia and leukopenia
c) includes Hepatobiliary Disorders preferred term of hyperbilirubinemia
d) includes Blood and Lymphatic System Disorders preferred term of thrombocytopenia
e) includes preferred terms: lung adenocarcinoma, lung adenocarcinoma metastatic, lung neoplasm malignant, lung squamous cell carcinoma stage unspecified, non-small cell lung cancer, small cell lung cancer stage unspecified
Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, Part 2 of 3

	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	2562
Total patients discontinuing due to AE	29 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Total number of AEs causing discont.	29	15	38	75	11	124	159
Gastrointestinal Disorders							
Total patients with at least one AE	**1 (<1)**	**5 (2)**	**1 (<1)**	**11 (1)**	**1 (<1)**	**13 (<1)**	**15 (1)**
GI perforation[f]	-	-	-	2	1	3	3
Abdominal pain	-	-	-	1	-	1	2
Dyspepsia/gastritis/GERD	-	-	-	2	-	2	2
GI ulcer[g]	1	-	-	2	-	2	1
Stomatitis/Mouth ulcer	-	1	-	2	-	2	1
GI bleeding[h]	-	1	1	-	-	1	2
Diarrhea	-	-	-	-	-	-	2
Irritable bowel syndrome	-	-	-	-	-	-	1
Colitis ischemic	-	-	-	-	-	-	1
Pancreatitis	-	-	-	1	-	1	-
Sigmoiditis	-	-	-	1	-	1	-
Crohn's disease	-	2	-	-	-	-	-
Nausea	-	1	-	-	-	-	-
Skin and Subcutaneous Tissue							
Total patients with at least one AE	**1 (<1)**	**0**	**3 (<1)**	**6 (<1)**	**0**	**9 (<1)**	**9 (<1)**
Rash	-	-	-	-	-	-	2
Dermatitis	-	-	1	-	-	1	1
Urticaria	-	-	-	1	-	1	1
Alopecia	-	-	1	-	-	1	1
Cutaneous vasculitis	1	-	-	1	-	1	1
Blister/skin ulcer	-	-	-	1	-	1	1
Skin fragility	-	-	-	-	-	-	1
Skin lesion	-	-	-	-	-	-	1
Erythema multiforme	-	-	-	1	-	1	-
Pyoderma gangrenosum	-	-	-	1	-	1	-
Pruritis	-	-	-	1	-	1	-
Drug eruption	-	-	1	-	-	1	-
Respiratory/Thoracic/Mediastinal							
Total patients with at least one AE	**1 (<1)**	**0**	**1 (<1)**	**1 (<1)**	**0**	**2 (<1)**	**11 (<1)**
Interstitial lung disease	-	-	-	-	-	-	2
Pulmonary fibrosis, idiopathic or NOS	-	-	-	1	-	1	2
Asthma	-	-	-	-	-	-	1
COPD	-	-	-	-	-	-	1
Dyspnea	-	-	-	-	-	-	1
Pleural effusion	-	-	-	-	-	-	1
Pneumonitis	-	-	-	-	-	-	1
Pulmonary embolism	-	-	-	-	-	-	1
Acute respiratory distress syndrome	-	-	-	-	-	-	1
Rheumatoid lung	-	-	1	-	-	1	-
Wegener's granulomatosis	1	-	-	-	-	-	-
Immune System Disorders							
Total patients with at least one AE	**0**	**1 (<1)**	**3 (<1)**	**3 (<1)**	**0**	**6 (<1)**	**3 (<1)**
Anaphylactic reaction	-	-	2	1	-	3	2
Hypersensitivity	-	-	1	2	-	3	1
Sarcoidosis	-	1	-	-	-	-	-
Nervous System Disorders							
Total patients with at least one AE	**2 (<1)**	**0**	**1 (<1)**	**3 (<1)**	**1 (<1)**	**5 (<1)**	**4 (<1)**
Axonal neuropathy	-	-	-	-	-	-	2
Demyelination	-	-	-	-	-	-	1
Migraine	-	-	-	1	-	1	1
CVA	-	-	-	1	-	1	-
Hemorrhagic stroke	-	-	-	1	-	1	-
Headache	-	-	-	-	1	1	-
Syncope	-	-	1	-	-	1	-
Facial palsy	1	-	-	-	-	-	-
Paresthesia	1	-	-	-	-	-	-

* Includes MTX
Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population
Multiple occurrences of the same AE in one individual are counted only once
Events on escape therapy are excluded
f) includes preferred terms: diverticular perforation, gastrointestinal perforation, large intestine perforation
g) includes preferred terms: duodenal ulcer, gastric ulcer, large intestinal ulcer
h) includes preferred terms: rectal hemorrhage, melena, GI hemorrhage
i) includes preferred terms: rheumatoid vasculitis, vasculitis, vasculitis necrotising
Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, Part 3 of 3

	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	2562
Total patients discontinuing due to AE	29 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Total number of AEs causing discont.	29	15	38	75	11	124	159
Cardiac Disorders							
Total patients with at least one AE	**1 (<1)**	**0**	**0**	**1 (<1)**	**1 (<1)**	**2 (<1)**	**6 (<1)**
Myocardial infarction/AMI	-	-	-	-	-	-	3
Cardiac failure	-	-	-	-	-	-	1
Aortic valve stenosis	-	-	-	-	-	-	1
Palpitations	-	-	-	-	-	-	1
Acute coronary syndrome	-	-	-	1	-	1	-
Myocardial ischemia	-	-	-	-	1	1	-
Coronary artery thrombosis	1	-	-	-	-	-	-
Hepatobiliary Disorders							
Total patients with at least one AE	**0**	**0**	**0**	**1 (<1)**	**2 (<1)**	**3 (<1)**	**3 (<1)**
Cholecystitis, acute	-	-	-	-	1	1	1
Hepatic steatosis	-	-	-	-	-	-	2
Hepatotoxicity	-	-	-	1	-	1	-
Liver disorder	-	-	-	-	1	1	-
Vascular Disorders							
Total patients with at least one AE	**2 (<1)**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**4 (<1)**
Vasculitis[i]	-	-	-	-	-	-	3
Deep vein thrombosis	2	-	1	-	-	1	1
Musculoskeletal and Connective Tissue							
Total patients with at least one AE	**6 (<1)**	**0**	**2 (<1)**	**0**	**1 (<1)**	**3 (<1)**	**2 (<1)**
Rheumatoid arthritis flare	4	-	2	-	-	2	2
Systemic Lupus Erythematosus	-	-	-	-	1	1	-
Pseudoarthrosis	1	-	-	-	-	-	-
Rheumatoid nodule	1	-	-	-	-	-	-
General Disorders/Admin. Site							
Total patients with at least one AE	**3 (<1)**	**0**	**1 (<1)**	**1 (<1)**	**1 (<1)**	**3 (<1)**	**1 (<1)**
Infusion related reaction	1	-	-	1	1	2	-
Chest discomfort/pain (non-cardiac)	-	-	1	-	-	1	1
Pyrexia	2	-	-	-	-	-	-
Pregnancy/Puerperium/Perinatal							
Total patients with at least one AE	**1 (<1)**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**3 (<1)**
Pregnancy	1	-	-	-	-	-	3
Induced abortion	-	-	1	-	-	1	-
Injury/Poison./Procedural Complic.							
Total patients with at least one AE	**0**	**0**	**1 (<1)**	**2 (<1)**	**0**	**3 (<1)**	**1 (<1)**
Fall	-	-	1	1	-	2	-
Femur fracture	-	-	-	1	-	1	-
Joint dislocation	-	-	-	-	-	-	1
Psychiatric Disorders							
Total patients with at least one AE	**0**	**1 (<1)**	**0**	**0**	**0**	**0**	**2 (<1)**
Completed suicide	-	-	-	-	-	-	1
Depression	-	-	-	-	-	-	1
Schizophrenia	-	1	-	-	-	-	-
Renal and Urinary Disorders							
Total patients with at least one AE	**0**	**0**	**0**	**0**	**0**	**0**	**2 (<1)**
Renal failure acute	-	-	-	-	-	-	1
IgA nephropathy, proliferative	-	-	-	-	-	-	1
Blood and Lymphatic System Disorders							
Total patients with at least one AE	**0**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**0**
Lymphadenopathy	-	-	1	-	-	1	-
Metabolism and Nutrition Disorders							
Total patients with at least one AE	**0**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**0**
Gout	-	-	1	-	-	1	-

* Includes MTX
Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population
Multiple occurrences of the same AE in one individual are counted only once
Events on escape therapy are excluded
i) includes preferred terms: rheumatoid vasculitis, vasculitis, vasculitis necrotising
Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update

7.3.4 Significant Adverse Events

GI Perforations

In the global RA TCZ program, to include the Roche and Chugai studies, as of December 31, 2007, approximately 4700 patients were exposed to TCZ for approximately 7961 patient-years cumulative exposure. A total of 16 GI perforation events occurred in 15 patients [one patient had both an upper GI (UGI) and a lower (LGI) event]. Compared to RA patients in the United Health Care database and the Marketscan database, RA patients in the TCZ global program had a slightly higher incidence of UGI perforation events and a similar incidence of LGI perforation events.

Almost all events occurred while patients were on TCZ 8 mg/kg, however TCZ 8 mg/kg was the default dose for the open-label extensions. The duration of TCZ exposure before event occurrence varied between 1 and 36 months. For additional details of the cases, refer to Table 27 below.

Table 26 Exposure Adjusted Incidence of GI Perforations

Exposure-Adjusted Incidence of GI Perforations in RA Patients				
	TCZ program Events	TCZ program Events/100 pt-yrs	UHC database Events/100 pt-yrs	Marketscan database Events/100 pt-yrs
Upper GI	4	0.05	0.03	0.02
Lower GI	12	0.15	0.16	0.14
Total	16	0.20	0.18	0.16

Data cut-off December 31, 2007

Sources: Tables 14 and 15 of 120 day safety update

Table 27 Line Listing of GI Perforations in the Tocilizumab Global Program

GI Perforations in the Tocilizumab Global Program								
Study	Event	Age/ Gender	TCZ dose	Doses prior to event	Latency (months)	Concomitant medications	Outcome	Comments
Roche Tocilizumab RA Pivotal Studies								
UGI Perforations								
WA17824	Duodenal perforation	76/F	8 mg/kg	2	1	ranitidine	death	
LGI Perforations								
WA18062	Diverticular perforation	82/F	8 mg/kg	2	1	pred/mtx	resolved	withdrawn
WA18063	Diverticular perforation	65/M	8 mg/kg	5	4	pred/mtx/asa salicylamide	resolved	withdrawn
WA18063/18696	Diverticular perforation	50/M	8 mg/kg	23	21	mtx/ssa/naproxen	resolved	withdrawn
WA18062/18696	Diverticular perforation abdominal wall abscess small bowel ischemia	60/F	8 mg/kg	8	8	mtx/pred	death	
WA18063/18696	Sealed divertic. perf.	65/F	8 mg/kg	18	21	mtx/pred/ssa ketoprofen/oxaprozin	resolved	
WA18063/18695	Diverticular perforation	67/F	8 mg/kg	33	31	mtx/pred	resolved	withdrawn
WA17822/18695	Diverticular perforation	67/M	8 mg/kg	28	27	mtx/pred	resolved	withdrawn
WA17823	Diverticular perforation abdominal abscess	66/F	blinded	11	9.5	indomethacin	resolved	withdrawn
WA18062/18696	Colon necrosis/perf.	48/F	4-8 mg/kg	19	24	mtx/pred diclofenac/tramadol	unknown	withdrawn
WA17823	Acute abdomen/free air	50/F	4-8 mg/kg	10	15	mtx/pred	resolved	unk source
Chugai Tocilizumab Studies								
UGI Perforations								
MRA012JP (RA)	Esophageal perforation (iatrogenic)	65/F	8 mg/kg	13	11	pred/lomoxicam	resolved	continued
MRA010JP (RA)	Duodenal perforation Sigmoid perforation	49/F	8 mg/kg	37	36	pred/etodolac teprenone	resolved/ improved	withdrawn
MRA011JP (SJIA)	Duodenal perforation	10/M	2-4-8 mg/kg q2wk	23	10.5	corticosteroids NSAIDs, PPIs	resolved	withdrawn
MRA006JP (Castleman's)	Gastric perforation	56/M	2-4-8 mg/kg q2wk	169	49	corticosteroids loxiprofen/famotidine	improved	continued
LGI Perforations								
MRA010JP (RA)	Sigmoid perforation		see above					
MRA214JP (RA)	Sigmoid perforation abdominal abscess	45/F	8 mg/kg	28	26	pred/diclofenac	resolved	withdrawn
Compassionate-use (RA)	Sigmoid perforation from diverticulitis	59/F	range	52	48	corticosteroids diclofenac/DMARDs	resolved	continued
MRA008JP (Crohn's)	Intestinal perforation	24/M	8 mg/kg q2wk	2	1	corticosteroids	resolved	pre-event colo:withdrawn

Source: Section 3.9.3.3 and Table 13 of 120 day safety update

Demyelinating Disorders

Four patients experienced demyelinating neurologic events in the global TCZ program, as detailed in Table 28, below. The background risk of demyelinating disorders in RA patients is not currently known.

Table 28 Line Listing of Demyelinating Adverse Events in the Tocilizumab Global Program

Demyelinating AEs in the Tocilizumab Global Program								
Study	Event	Age/ Gender	TCZ dose	Doses prior to event	Latency (months)	Concomitant diagnoses	Outcome	Comments
WA18062/18696	L sided pos Babinski & tremor; MRI c/w white matter lesions & parietal lobe atrophy	64/M	8 mg/kg	11 to 14 (escape at week 16)	14	migraines hypothyroid peripheral vascular dz	tremor dx'd as benign essential tx with topiramate	withdrawn
WA17823	Blurred vision, dx with cataracts and bilateral optic neuritis	73/F	Blinded	8	8	on INH for pos PPD HTN, osteoporosis	No other demyel. lesions on MRI	continued
WA18062/18696	Progressive weakness & wt loss, dx as chronic idiopathic polyradiculoneuropathy	68/F	8 mg/kg	~11	~10	COPD, HTN, HLD DVT, osteoporosis	death	
MRA213JP/ MRA215JP	deteriorating mental status, dx as leukoencephalopathy	72/F	8 mg/kg	50	~50	Type II DM, HTN HLD, aortic stenosis osteoporosis	extensive white matter lesions neg w/u (inc. PML)	withdrawn

Source: BLA 125276 amendment 11 case narratives

7.3.5 Submission Specific Primary Safety Concerns

See Summary of Safety Results and Conclusions above.

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

Overall, the types and incidence of common adverse events in the TCZ RA pivotal trials and long-term extensions were consistent with the patient population and the immunosuppressive nature of the study treatments. Frequency by system-organ-class and trial treatment is listed in Table 29, below. Infections/infestations were again the most common type of adverse event, followed by GI disorders. Table 30 below lists the common events by preferred term occurring in at least 1% of patients in a TCZ treatment group, where occurrence was greater in a TCZ group than placebo. Most events were typical, such as upper respiratory infections and headache. The possible relationship of TCZ treatment with events of hypertension and laboratory abnormalities are discussed in further detail below.

Table 29 Common Adverse Events by System-Organ-Class

Common Adverse Events in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by System Organ Class and Trial Treatment							
	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	2562
Patients with any AEs	733 (63)	220 (77)	547 (71)	1134 (72)	230 (80)	1911 (72)	2259 (88)
Infections and Infestations	365 (31)	106 (37)	266 (34)	581 (37)	96 (33)	943 (36)	1555 (61)
Gastrointestinal Disorders	191 (16)	89 (31)	164 (21)	342 (22)	86 (30)	592 (22)	1052 (41)
Skin and Subcutaneous	94 (8)	32 (11)	118 (15)	253 (16)	42 (15)	413 (16)	650 (25)
Musculoskeletal/Connective Tissue	173 (15)	32 (11)	98 (13)	187 (12)	33 (11)	318 (12)	793 (31)
Nervous System	104 (9)	18 (6)	90 (12)	193 (12)	37 (13)	320 (12)	561 (22)
Investigations	46 (4)	43 (15)	80 (10)	192 (12)	48 (17)	320 (12)	470 (18)
General/Admin site	91 (8)	24 (8)	74 (10)	133 (8)	21 (7)	228 (9)	386 (15)
Respiratory/Thoracic/Mediastinal	72 (6)	19 (7)	58 (7)	132 (8)	26 (9)	216 (8)	442 (17)
Injury/Poisoning/Procedural Comp.	67 (6)	15 (5)	50 (6)	114 (7)	14 (5)	178 (7)	439 (17)
Vascular	60 (5)	13 (5)	59 (8)	102 (6)	24 (8)	185 (7)	373 (15)
Psychiatric	35 (3)	11 (4)	33 (4)	57 (4)	20 (7)	110 (4)	232 (9)
Eye Disorders	28 (2)	9 (3)	23 (3)	62 (4)	15 (5)	100 (4)	244 (9)
Metabolism/Nutrition	32 (3)	5 (2)	27 (3)	55 (3)	8 (3)	90 (3)	268 (10)
Blood and Lymphatic	26 (2)	9 (3)	18 (2)	62 (4)	11 (4)	91 (3)	196 (8)
Reproductive/Breast	17 (1)	6 (2)	15 (2)	37 (2)	13 (5)	65 (2)	127 (5)
Cardiac	17 (1)	7 (2)	8 (1)	30 (2)	8 (3)	46 (2)	139 (5)
Renal/Urinary	21 (2)	5 (2)	11 (1)	30 (2)	10 (3)	51 (2)	105 (4)
Ear/Labyrinth	21 (2)	3 (1)	17 (2)	23 (1)	3 (1)	43 (2)	103 (4)
Neoplasms, benign/malignant/NOS	9 (1)	4 (1)	13 (2)	22 (1)	3 (1)	38 (1)	117 (5)
Hepatobiliary	4 (<1)	4 (1)	3 (<1)	16 (1)	9 (3)	28 (1)	61 (2)
Immune System Disorders	8 (1)	4 (1)	7 (1)	18 (1)	2 (1)	27 (1)	62 (2)
Surgical/Medical Procedures	5 (<1)	-	6 (1)	9 (<1)	2 (1)	17 (1)	53 (2)
Endocrine	1 (<1)	1 (<1)	3 (<1)	10 (1)	3 (1)	16 (1)	28 (1)
Congenital/Familial/Genetic	1 (<1)	-	3 (<1)	2 (<1)	-	5 (<1)	15 (1)
Pregnancy/Puerperium/Perinatal	2 (<1)	-	-	-	-	-	7 (<1)

*includes MTX

Data cut-off April 20, 2007 for 6 month safety population, October 1, 2007 for long-term safety population

Adapted from Table 50 of WA17822 CSR, Table 47 of WA17823 CSR, Table 61 of WA17824 CSR, Table 60 of WA18062 CSR, Table 52 of WA18063 CSR and Table stae11_1 of 120 day safety update

Table 30 Common Adverse Events by Preferred Terms

Common Adverse Events (≥1% in a TCZ group and greater than placebo) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Preferred Term and Trial Treatment							
	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	2562
Patients with any AEs	733 (63)	220 (77)	547 (71)	1134 (72)	230 (80)	1911 (72)	2259 (88)
Upper Respiratory Tract Infection	71 (6)	15 (5)	48 (6)	123 (8)	21 (7)	192 (7)	398 (16)
Headache	40 (3)	7 (2)	45 (6)	84 (5)	21 (7)	150 (6)	252 (10)
Nasopharyngitis	52 (4)	17 (6)	33 (4)	88 (6)	20 (7)	141 (5)	309 (12)
Hypertension	32 (3)	6 (2)	32 (4)	70 (4)	16 (6)	118 (4)	243 (9)
Nausea	44 (4)	34 (12)	33 (4)	63 (4)	18 (6)	114 (4)	186 (7)
Diarrhea	38 (3)	15 (5)	31 (4)	61 (4)	15 (5)	107 (4)	243 (9)
Bronchitis	38 (3)	6 (2)	33 (4)	51 (3)	9 (3)	93 (4)	225 (9)
Rash	15 (1)	4 (1)	30 (4)	52 (3)	7 (2)	89 (3)	142 (6)
ALT Increased	10 (1)	11 (4)	22 (3)	50 (3)	16 (6)	88 (3)	103 (4)
Urinary Tract Infection	39 (3)	13 (5)	17 (2)	53 (3)	12 (4)	82 (3)	208 (8)
Back Pain	28 (2)	3 (1)	16 (2)	52 (3)	7 (2)	75 (3)	173 (7)
Dizziness	20 (2)	4 (1)	15 (2)	49 (3)	9 (3)	73 (3)	115 (4)
Sinusitis	24 (2)	11 (4)	16 (2)	46 (3)	9 (3)	71 (3)	178 (7)
Dyspepsia	23 (2)	12 (4)	17 (2)	41 (3)	10 (3)	68 (3)	155 (6)
Abdominal Pain Upper	18 (2)	6 (2)	21 (3)	39 (2)	5 (2)	65 (2)	124 (5)
Cough	22 (2)	1 (<1)	16 (2)	36 (2)	8 (3)	60 (2)	132 (5)
Transaminases Increased	6 (<1)	13 (5)	13 (2)	37 (2)	3 (1)	53 (2)	74 (3)
Pharyngolaryngeal Pain	13 (1)	3 (1)	15 (2)	27 (2)	7 (2)	49 (2)	92 (4)
Edema, Peripheral	17 (1)	-	10 (1)	33 (2)	5 (2)	48 (2)	99 (4)
Mouth Ulceration	6 (<1)	6 (2)	10 (1)	31 (2)	6 (2)	47 (2)	81 (3)
Gastroenteritis	17 (1)	9 (3)	18 (2)	24 (2)	4 (1)	46 (2)	116 (5)
Abdominal Pain	15 (1)	6 (2)	13 (2)	21 (1)	11 (4)	45 (2)	100 (4)
Pruritis	11 (1)	3 (1)	11 (1)	25 (2)	8 (3)	44 (2)	52 (2)
Gastritis	9 (1)	5 (2)	9 (1)	28 (2)	3 (1)	40 (2)	77 (3)
Insomnia	15 (1)	3 (1)	16 (2)	16 (1)	6 (2)	38 (1)	85 (3)
Hepatic Enzyme Increased	7 (1)	8 (3)	9 (1)	23 (1)	6 (2)	38 (1)	62 (2)
Depression	14 (1)	2 (1)	8 (1)	20 (1)	6 (2)	34 (1)	67 (3)
Alopecia	6 (<1)	8 (3)	6 (1)	16 (1)	6 (2)	28 (1)	64 (2)
Leukopenia	1 (<1)	-	4 (<1)	19 (1)	4 (1)	27 (1)	50 (2)
Anxiety	9 (1)	2 (1)	5 (1)	13 (1)	7 (2)	25 (1)	51 (2)
Gastroenteritis, Viral	7 (1)	4 (1)	7 (1)	12 (1)	5 (2)	24 (1)	53 (2)
Conjunctivitis	6 (<1)	1 (<1)	5 (1)	15 (1)	4 (1)	24 (1)	58 (2)
Neutropenia	-	-	3 (<1)	17 (1)	4 (1)	24 (1)	63 (2)
Rhinitis	6 (<1)	6 (2)	11 (1)	10 (1)	2 (1)	23 (1)	46 (2)
Dyspnea	3 (<1)	1 (<1)	8 (1)	13 (1)	1 (<1)	22 (1)	38 (1)
Weight Increased	2 (<1)	1 (<1)	5 (1)	12 (1)	5 (2)	22 (1)	41 (2)
Stomatitis	3 (<1)	5 (2)	4 (<1)	12 (1)	4 (1)	20 (1)	34 (1)
Cystitis	4 (<1)	2 (1)	9 (1)	9 (1)	2 (1)	20 (1)	49 (2)
Hypercholesterolemia	0	1 (<1)	2 (<1)	17 (1)	1 (<1)	20 (1)	90 (4)
Gastroesophageal Reflux Disease	6 (<1)	6 (2)	5 (1)	13 (1)	1 (<1)	19 (1)	58 (2)
Chest Pain	6 (<1)	3 (1)	6 (1)	8 (<1)	4 (1)	18 (1)	27 (1)
Liver Function Test Abnormal	3 (<1)	4 (1)	7 (1)	9 (1)	2 (1)	18 (1)	29 (1)
Paresthesia	6 (<1)	-	3 (<1)	10 (1)	3 (1)	16 (1)	42 (2)
Dysuria	8 (1)	1 (<1)	3 (<1)	7 (<1)	5 (2)	15 (1)	20 (1)
Musculoskeletal Pain	5 (<1)	1 (<1)	6 (1)	6 (<1)	3 (1)	15 (1)	51 (2)
Epistaxis	1 (<1)	4 (1)	2 (<1)	12 (1)	1 (<1)	15 (1)	24 (1)
Flushing	4 (<1)	1 (<1)	5 (1)	5 (<1)	3 (1)	13 (<1)	14 (1)
AST Increased	1 (<1)	1 (<1)	3 (<1)	5 (<1)	5 (2)	13 (<1)	20 (1)
Hypoesthesia	3 (<1)	1 (<1)	4 (<1)	4 (<1)	3 (1)	11 (<1)	22 (1)
Osteoarthritis	4 (<1)	-	2 (<1)	5 (<1)	4 (1)	11 (<1)	37 (1)
Menorrhagia	3 (<1)	1 (<1)	2 (<1)	5 (<1)	3 (1)	10 (<1)	14 (<1)
Hyperlipidemia	3 (<1)	-	3 (<1)	3 (<1)	4 (1)	10 (<1)	44 (2)
Neutrophil Count Decreased	-	-	2 (<1)	4 (<1)	3 (1)	9 (<1)	18 (1)
Palpitations	6 (<1)	3 (1)	2 (<1)	4 (<1)	2 (1)	8 (<1)	27 (1)
Abdominal Discomfort	2 (<1)	-	2 (<1)	3 (<1)	3 (1)	8 (<1)	23 (1)
Blood Triglycerides Increased	-	-	-	5 (<1)	3 (1)	8 (<1)	24 (1)

*includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

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

Events on escape therapy are excluded.

Adapted from Table stae13_1 of Module 2.7.4 and Table stae11_1 of 120 day safety update.

7.4.2 Laboratory Findings

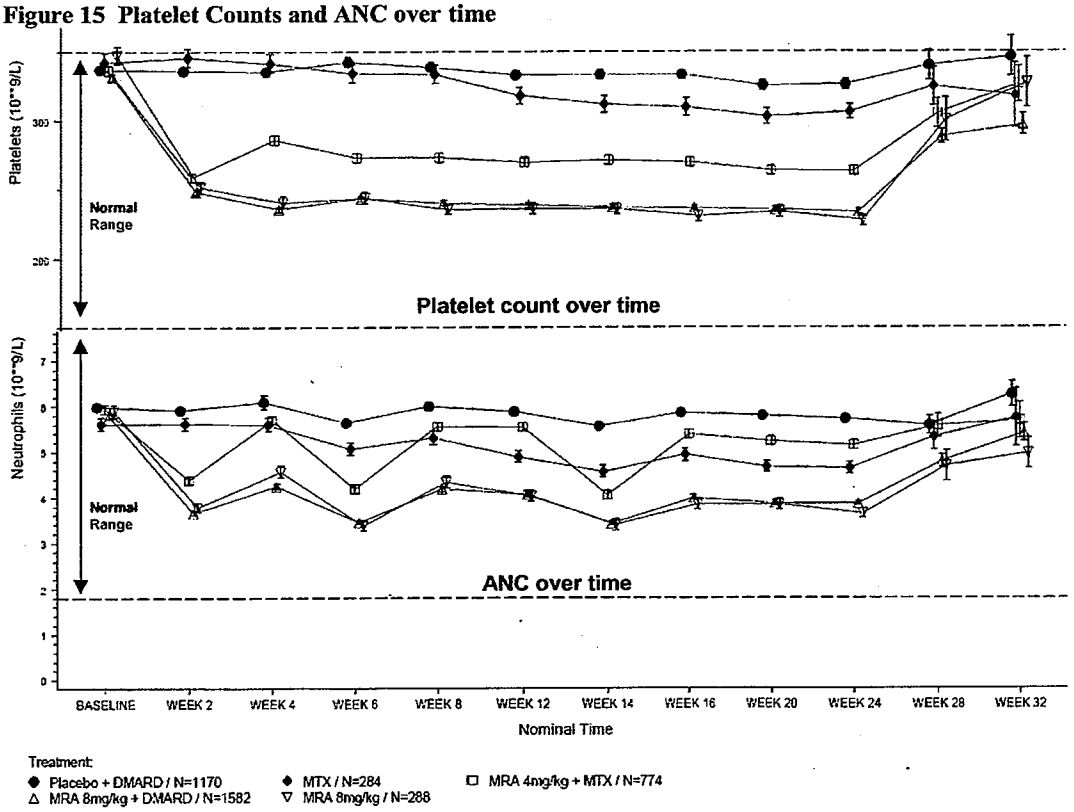
Treatment with TCZ appeared to result in dose-related changes in certain hematology, hepatobiliary and lipid parameters. Mean changes from baseline are summarized in Table 31, below; changes in absolute neutrophil count (ANC) and platelets are illustrated in Figure 15, below. Overall, neutrophil counts and platelet counts remained within the normal range and reverted back toward baseline once treatment ended (at Week 24). TCZ treatment resulted in small mean increases in liver enzyme tests and possibly bilirubin. Changes in lipid parameters were also incrementally small; however all lipid parameters, including total cholesterol, HDL, LDL and triglycerides were increased. Changes of greater magnitude are discussed in further detail below.

Table 31 Mean Change from Baseline in Hematology, Hepatobiliary, and Lipid Parameters

Mean Change from Baseline in Selected Laboratory Parameters at Week 24 in the Tocilizumab RA Pivotal Studies							
		6-months pooled safety population					
	normal range	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ
Enrolled		1170	284	774	1582	288	2644
Hematology							
WBC (10^9/L)	(4.5-11.0)	-0.1	-1.1	-0.8	-1.9	-2.2	-1.7
Neutrophils (10^9/L)	(1.8-7.7)	-0.1	-1.0	-0.8	-1.9	-2.2	-1.7
Lymphocytes (10^9/L)	(1.0-4.8)	-0.9	-0.02	-0.03	0.02	0.1	0.01
Platelets (10^9/L)	(150-350)	-5	-37	-75	-98	-119	-94
Hemoglobin (g/L)	(130-180)	-1	2	6	11	13	10
Hepatobiliary							
AST (U/L)	(0-40)	0	3	3	7	6	6
ALT (U/L)	(0-55)	2	8	9	16	13	14
Total Bilirubin (umol/L)	(0-17)	0	1	2	3	3	3
Alkaline Phosphatase (U/L)	(0-115)	-1	-2	-12	-20	-20	-18
Lipids							
Cholesterol (mmol/L)	(0-6.18)	0.10	0.19	0.42	0.77	0.96	0.70
HDL (mmol/L)	(0.91-n.d.)	0.02	0.08	0.08	0.13	0.11	0.11
LDL (mmol/L)	(0-4.13)	0.05	0.13	0.31	0.52	0.68	0.48
Triglycerides (mmol/L)	(0.45-1.69)	0.02	-0.05	0.09	0.32	0.44	0.27
Total Cholesterol/HDL ratio	(n.d.-5.00)	0.01	-0.09	0.14	0.25	0.46	0.24
LDL/HDL ratio	(n.d.-7.10)	0	-0.03	0.12	0.16	0.31	0.17

*Includes MTX
Worst values within a time window per patient are summarized
Escape data is excluded
Adapted from Table 41 and Table stlb10_sum of Module 2.7.4

Figure 15 Platelet Counts and ANC over time



Only worst values within a time window per patient are summarized. Escape data excluded.
Taken from Figures 2 and 3 of Module 2.7.4 Summary of Clinical Safety

Marked Laboratory Abnormalities

Hematology parameters:

As noted in Table 32 below, few patients reached the protocol-mandated discontinuation point of ANC $\leq 0.5 \times 10^9$/L during the 6-month controlled period, however those who did were on TCZ treatment. Discontinuation criteria were not pre-specified for other hematology parameters. A higher proportion of TCZ-treated patients met protocol-defined criteria for markedly low WBC or neutrophils, however these low white blood cell counts were not associated with infectious adverse events. Similarly, a higher proportion of TCZ-treated patients met protocol-defined criteria for at least one markedly low platelet count, but few of these patients had replicated values meeting these criteria. Low platelet counts were not associated with bleeding adverse events.

Table 32 Markedly Abnormal Hematology Parameters

Markedly Abnormal Hematology Parameters in the Tocilizumab RA Pivotal Studies and Long-Term Extensions									
			6-months pooled safety population						Long term safety population
	normal range	markedly abnl def.	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	2562
Pts discontinued for abnl			-	-	3 (<1)	7 (<1)	1 (<1)	11 (<1)	10 (<1)
Dose mod/interrupted			-	1 (<1)	3 (<1)	9 (1)	7 (2)	19 (1)	74 (3)
WBC (10^9/L), low	(4.5-11.0)	<3, >18							
single, not last value			9 (<1)	3 (1)	28 (4)	98 (6)	7 (2)	133 (5)	168 (7)
last value or replicated			1 (<1)	3 (1)	8 (1)	53 (3)	5 (2)	66 (3)	112 (4)
any value			10 (<1)	6 (2)	36 (5)	151 (10)	12 (4)	199 (8)	280 (11)
Neutrophils (10^9/L), low	(1.8-7.7)	<1.5, >9.25							
single, not last value			9 (<1)	4 (1)	55 (7)	141 (9)	22 (8)	218 (8)	264 (10)
last value or replicated			1 (<1)	3 (1)	14 (2)	90 (6)	17 (6)	121 (5)	202 (8)
any value			10 (<1)	7 (2)	69 (9)	231 (15)	39 (14)	339 (13)	466 (18)
Lymphocytes (10^9/L), low	(1.0-4.8)	<0.7, >7.6							
single, not last value			46 (4)	12 (4)	35 (5)	49 (3)	5 (2)	89 (3)	127 (5)
last value or replicated			22 (2)	3 (1)	10 (1)	22 (1)	1 (<1)	33 (1)	46 (2)
any value			68 (6)	15 (5)	45 (6)	71 (4)	6 (2)	122 (5)	173 (7)
Platelets (10^9/L), low	(150-350)	<100, >550							
single, not last value			2 (<1)	-	7 (<1)	20 (1)	2 (<1)	29 (1)	33 (1)
last value or replicated			4 (<1)	-	3 (<1)	7 (<1)	2 (<1)	12 (<1)	26 (1)
any value			6 (<1)	-	10 (1)	27 (2)	4 (1)	41 (2)	59 (2)
Hemoglobin (g/L), low	(130-180)	<110, >200							
single, not last value			29 (2)	15 (5)	5 (<1)	11 (<1)	-	16 (<1)	34 (1)
last value or replicated			37 (3)	7 (2)	13 (2)	14 (<1)	1 (<1)	28 (1)	38 (<1)
any value			66 (6)	22 (8)	18 (2)	25 (2)	1 (<1)	44 (2)	72 (3)

*Includes MTX
Worst values within a time window per patient are summarized
Escape data is excluded
Sources: Table stb10_mark of Module 2.7.4, Pg. 94 and Tables stae11_wd, stae11_dmod, stb10_lcl_ssta and stb10_mark of 120 day safety update

Hepatobiliary parameters:

Per protocol, patients experiencing 2 transaminase elevations ≥3 X ULN on treatment were permanently discontinued from study drug. Patients experiencing any transaminase elevations > 5 X ULN or total bilirubin >2.5 mg/dL or unconjugated bilirubin levels > 2 X ULN were also to be permanently discontinued from study drug in the core studies. The number of patients actually discontinued for these reasons was low, but the proportion was higher in the TCZ treatment groups, as summarized in Table 33, below. Dose modification or interruption for hepatobiliary laboratory abnormalities was also more frequent in the TCZ treatment groups compared with placebo, although was also increased with MTX.

Overall, TCZ treatment was associated with a higher incidence of markedly abnormal (as defined by the applicant) AST/ALT elevation. The highest incidence, particularly of ALT elevation, was observed in the TCZ 8 mg/kg + DMARD group of the controlled period and in the long-term extension studies. The TCZ 4 mg/kg + MTX and MTX monotherapy groups were slightly lower in incidence but still elevated compared to the placebo control group. The incidence was yet lower in the TCZ 8 mg/kg monotherapy group but was also still elevated compared to the placebo group.

Table 33 Markedly Abnormal Hepatobiliary Parameters

Markedly Abnormal Hepatobiliary Parameters in the Tocilizumab RA Pivotal Studies and Long-Term Extensions									
			6-months pooled safety population						Long term safety population
	normal range	markedly abnl def.	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	2562
Pts discontinued for abnl			**2 (<1)**	**4 (1)**	**12 (2)**	**28 (2)**	**1 (<1)**	**41 (2)**	**26 (1)**
Dose mod/interrupted			**8 (1)**	**24 (8)**	**19 (2)**	**37 (2)**	**22 (8)**	**78 (3)**	**151 (6)**
AST (U/L)	(0-40)	>80							
single, not last value			10 (<1)	12 (4)	30 (4)	59 (4)	5 (2)	94 (4)	148 (6)
last value or replicated			3 (<1)	2 (<1)	7 (<1)	35 (2)	0	42 (2)	52 (2)
any value			13 (1)	14 (5)	37 (5)	94 (6)	5 (2)	136 (5)	200 (8)
ALT (U/L)	(0-55)	>110							
single, not last value			39 (3)	22 (8)	67 (9)	139 (9)	16 (6)	222 (8)	297 (12)
last value or replicated			16 (1)	11 (4)	34 (4)	123 (8)	12 (4)	169 (6)	209 (8)
any value			55 (5)	33 (12)	101 (13)	262 (17)	28 (10)	391 (15)	506 (20)
Total Bilirubin (umol/L)	(0-17)	>34							
single, not last value			1 (<1)	0	2 (<1)	8 (<1)	0	10 (<1)	15 (<1)
last value or replicated			0	0	2 (<1)	4 (<1)	0	6 (<1)	8 (<1)
any value			1 (<1)	0	2 (<1)	12 (<1)	0	16 (<1)	23 (<1)
Alkaline Phosphatase (U/L)	(0-115)	>220							
single, not last value			6 (<1)	4 (1)	1 (<1)	5 (<1)	1 (<1)	7 (<1)	11 (<1)
last value or replicated			2 (<1)	2 (<1)	2 (<1)	2 (<1)	0	4 (<1)	2 (<1)
any value			8 (<1)	6 (2)	3 (<1)	7 (<1)	1 (<1)	11 (<1)	13 (<1)

*Includes MTX
Worst values within a time window per patient are summarized
Escape data is excluded
Sources: Table stlb10_mark of Module 2.7.4, Pg. 94 and Tables stae11_wd, stae11_dmod, stlb10_ldl_ssta and stlb10_mark of 120 day safety update

Table 34 below summarizes the hepatobiliary worst values in the tocilizumab studies by treatment group. A small percentage of patients experienced elevations in AST or ALT above 3 x ULN, or abnormal total bilirubin. A higher proportion of patient experienced AST and ALT abnormalities in the tocilizumab combination therapy groups, across the range from mild to more significant abnormalities. A higher percentage of patients in these two groups also experienced elevations in total bilirubin. However, no instances of liver enzyme elevations to >3 X ULN with concomitant increase in total bilirubin to >2 X ULN were noted in the 6-months safety population.

Table 34 Hepatobiliary Worst Values

Hepatobiliary Worst Values in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
		6-months pooled safety population						Long term safety population
	range	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	2562
AST (U/L)								
normal	0-40	967 (83)	201 (71)	498 (64)	902 (57)	220 (76)	1620 (61)	1319 (51)
>ULN to 3 x ULN	41-120	194 (17)	74 (26)	264 (34)	646 (41)	64 (22)	974 (37)	1176 (46)
>3 x ULN to 5 x ULN	121-200	3 (0.3)	5 (2)	8 (1)	29 (2)	1 (0.3)	38 (1)	53 (2)
>5 x ULN to 8 x ULN	201-320	-	1 (0.4)	1 (0.1)	1 (0.1)	1 (0.3)	3 (0.1)	7 (0.3)
>8 x ULN	>320	1 (0.1)	-	-	2 (0.1)	1 (0.3)	3 (0.1)	2 (0.1)
ALT (U/L)								
normal	0-55	877 (75)	172 (61)	376 (49)	714 (45)	176 (61)	1266 (48)	991 (39)
>ULN to 3 x ULN	56-165	270 (23)	95 (33)	349 (45)	763 (48)	105 (36)	1217 (46)	1370 (53)
>3 x ULN to 5 x ULN	166-275	15 (1)	11 (4)	36 (5)	80 (5)	4 (1)	120 (5)	170 (7)
>5 x ULN to 8 x ULN	276-440	1 (0.1)	2 (0.7)	10 (1)	21 (1)	1 (0.3)	32 (1)	20 (0.8)
>8 x ULN	>440	2 (0.2)	1 (0.4)	-	2 (0.1)	1 (0.3)	3 (0.1)	7 (0.3)
Total Bilirubin (umol/L)								
normal	0-17	1155 (99)	279 (98)	724 (94)	1438 (91)	264 (92)	2426 (92)	2250 (88)
>ULN to 3 x ULN	18-51	9 (0.8)	2 (0.7)	46 (6)	141 (9)	23 (8)	210 (8)	308 (12)
>3 x ULN to 5 x ULN	52-85	1 (0.1)	-	-	1 (0.1)	-	1 (0.03)	-
>5 x ULN to 8 x ULN	86-136	-	-	-	-	-	-	-
>8 x ULN	>136	-	-	1 (0.1)	-	-	1 (0.03)	-

*Includes MTX
Escape data are excluded
Sources: Tables stlb_shift_btow_bchem of Module 2.7.4 Summery of Clinical Safety and 120 day safety update

The pattern of liver enzyme elevations was very similar in the methotrexate and TCZ 8 mg/kg monotherapy treatment arms of study 17824, where both monotherapy arms showed fewer instances of liver enzyme elevation compared to the tocilizumab combination treatment groups. However, TCZ 8 mg/kg monotherapy was associated with a higher rate of total bilirubin elevation to up to 3x ULN

Overall, in patients experiencing liver enzyme elevations who continued on study, modification of treatment regimen (a reduction of the dose of DMARD, an interruption of TCZ infusion and/or reduction of TCZ dose from 8 mg/kg to 4 mg/kg) led to a decrease or a normalization without subsequent elevation of liver enzymes, or occurrence of hepatobiliary AEs. Currently available data on over 3700 patients treated with TCZ for up to 2 years contain no clinical events of hepatitis or hepatic failure.

Single Hy's Law Case:

Hy's law has been utilized by FDA to identify drugs likely to be capable of causing severe liver injury. Hy's law is based on the observation by the eponymous Dr. Hy Zimmerman that drug-induced jaundice caused by hepatocellular injury, and without an obstructive component, has a high rate of bad outcomes; approximately 10-50% mortality, in the era before liver transplant.

The components of Hy's law are a combination of transaminase elevation to greater than 3 x ULN and total bilirubin greater than 2 x ULN, and no evidence of biliary obstruction, such as elevated alkaline phosphatase, or Gilbert's syndrome. Based on original estimates of mortality, severe drug-induced liver injury can be estimated to occur at a rate of at least 1/10th the rate of Hy's law cases.

A single Hy's law case was identified in the tocilizumab global RA program, and occurred in the long-term extension of the Roche RA studies submitted in this application. The patient is a female in her late 50's, who completed 6 months of TCZ 8 mg/kg monotherapy with only isolated increases in total bilirubin to greater than 1 X ULN and without simultaneous increase in transaminases or alkaline phosphatase. She enrolled in the long-term extension and began MTX at 20 mg weekly without dose titration, in addition to treatment with open-label TCZ at 8 mg/kg.

At Week 5 of the LTE, the patient was noted to have elevated AST to 2 x ULN, elevated ALT to 4 x ULN, and elevated total bilirubin to less than 2 x ULN. 2 doses of MTX and 1 dose of TCZ were skipped, but by week 9, the patient's AST peaked at greater than 10 x ULN, ALT at greater than 16 x ULN, and total bilirubin at greater than 2 x ULN. Alkaline phosphatase levels remained in the normal range during the episode, although one subsequent alkaline phosphatase level was slightly elevated (130 with normal range 35-123 U/L). TCZ and MTX were withheld, and elevations ultimately normalized by week 12. At Week 11, MTX was re-started at 10 mg/week, and with normalized enzymes, the patient was re-started on TCZ 4 mg/kg at Week 12. By Week 15, the

patient's transaminases and bilirubin were again above the upper limit of normal and the patient was discontinued from study treatment and withdrawn from the study. These abnormalities resolved by Week 20; the patient did not have clinical adverse events associated with these laboratory abnormalities.

This case was confounded by the concomitant initiation of relatively high dose methotrexate, which has known hepatotoxicity, but also demonstrated positive re-challenge to TCZ. This single case, occurring in approximately 4700 patients in the TCZ global RA program, using the estimate of severe drug-induced liver injury as occurring at 1/10th the rate of Hy's law cases, could portend 1 anticipated case of severe liver injury in 47,000 treated patients.

Although the mechanism of action of liver enzyme abnormalities with tocilizumab has not been ascertained, there are plausible mechanisms by which hepatocellular injury could occur with anti-IL6R treatment. First, IL6 appears to have a hepatoprotective effect on various forms of liver injury and promotes hepatocyte regeneration. Therefore inhibition could lead to increased hepatocyte susceptibility to hepatotoxic insults. Also, hepatocytes express high levels of IL6 receptor; which raises the question of whether, with ubiquitous anti-IL6R monoclonal antibody binding in the liver, even minimal complement-mediated cytotoxicity or antibody-dependent cellular cytotoxicity could result in some hepatic injury.

No clinical events of hepatitis or hepatic failure have occurred in the closely monitored setting of the tocilizumab clinical trial program. However the abnormalities in liver enzymes observed, including the single Hy's law case identified, raise a sufficient level of concern to warrant inclusion of monitoring and dose modification recommendations in labeling.

Lipid parameters

As shown below in Table 35, very few patients experienced markedly low HDLs, however a higher proportion of patients in the TCZ treatment groups met applicant-defined criteria for markedly abnormal elevations in total cholesterol, LDL, and triglycerides. Lipid-lowering agents could be initiated at the discretion of patients' health care providers but were not mandated in the study protocols. The proportion of patients started on lipid-lowering agents in the RA pivotal trials/extensions (1-2% in the controlled period, 7% in the long-term extensions) does not appear to be excessive, given the underlying cardiovascular risk and co-morbidities in the RA patient population. Cardiovascular events have been discussed above in the serious adverse events section; thus far, MI and CVA rates in the RA pivotal studies/extensions are not elevated compared to rates described in the literature.

Table 35 Markedly Abnormal Lipid Parameters

Markedly Abnormal Lipid Parameters in the Tocilizumab RA Pivotal Studies and Long-Term Extensions									
			6-months pooled safety population						Long term safety population
	normal range	markedly abnl def.	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	2562
Pts discontinued for abnl			-	-	-	-	-	-	1 (<1)
Dose mod/interrupted			-	-	-	-	-	-	5 (<1)
Lipid lowering agent started			13 (1)	2 (1)	15 (2)	19 (1)	3 (1)	37 (1)	180 (7)
Cholesterol (mmol/L)	(0-6.18)	>8.30							
single, not last value			1 (<1)	2 (<1)	14 (2)	30 (2)	11 (4)	55 (2)	103 (4)
last value or replicated			1 (<1)	0	6 (<1)	28 (2)	12 (4)	46 (2)	82 (3)
any value			2 (<1)	2 (<1)	20 (3)	58 (4)	23 (8)	101 (4)	185 (7)
HDL (mmol/L)	(0.91-n.d.)	<0.65							
single, not last value			0	0	0	1 (<1)	2 (<1)	3 (<1)	10 (<1)
last value or replicated			1 (<1)	1 (<1)	2 (<1)	1 (<1)	0	3 (<1)	5 (<1)
any value			1 (<1)	1 (<1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	15 (<1)
LDL (mmol/L)	(0-4.13)	>5.4							
single, not last value			3 (<1)	3 (1)	17 (2)	37 (2)	12 (4)	66 (3)	128 (5)
last value or replicated			3 (<1)	1 (<1)	13 (2)	58 (4)	17 (6)	88 (3)	144 (6)
any value			6 (<1)	4 (1)	30 (4)	95 (6)	29 (11)	154 (6)	272 (11)
Triglycerides (mmol/L)	(0.45-1.69)	>2.83							
single, not last value			7 (<1)	1 (<1)	38 (5)	77 (5)	20 (7)	135 (5)	245 (10)
last value or replicated			9 (<1)	0	23 (3)	77 (5)	19 (7)	119 (5)	185 (7)
any value			16 (1)	1 (<1)	61 (8)	154 (10)	39 (14)	254 (10)	430 (17)

*Includes MTX
Worst values within a time window per patient are summarized
Escape data is excluded
Sources: Table stlb10_mark of Module 2.7.4, Pg. 94 and Tables stae11_wd, stae11_dmod, stlb10_ldl_ssta and stlb10_mark of 120 day safety update

7.4.3 Vital Signs

A higher proportion of patients in the TCZ treatment groups experienced elevations of 20 mmHg or more in systolic and/or diastolic blood pressure, summarized in Table 36, below. Blood pressure elevation was transient, and no permanent changes were noted, as evidenced by lack of change in baseline vs. last post-baseline mean blood pressures. The few HTN-related SAEs reported during the 6-month controlled period occurred in the TCZ 8 mg/kg + DMARD treatment arm; however, as previously noted, exposure-adjusted rates of stroke events overall are within expected rates for the RA patient population.

Table 36 Effect of Tocilizumab on Blood Pressure

Effect of Tocilizumab on Blood Pressure (6 Month Pooled Safety Population) by Trial Treatment					
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg
Enrolled	1170	284	774	1582	288
Highest BP reading (mmHg)	n (%)	n (%)	n (%)	n (%)	n (%)
Systolic BP					
>150 and ↑ by >10 to ≤20	109 (9)	24 (8)	49 (6)	150 (9)	30 (10)
>150 and ↑ by >20	137 (12)	30 (11)	94 (12)	238 (15)	43 (15)
Diastolic BP					
>90 and ↑ by >10 to ≤20	125 (11)	31 (11)	93 (12)	235 (15)	40 (14)
>90 and ↑ by >20	73 (6)	10 (4)	62 (8)	129 (8)	29 (10)
HTN-related AEs reported	n (%)	n (%)	n (%)	n (%)	n (%)
Infusion-related hypertension	10 (1)	2 (1)	7 (1)	17 (1)	7 (2)
Hypertension NOS	32 (3)	6 (2)	32 (4)	70 (4)	16 (6)
SAE, Hypertension	-	-	-	1 (<1)	-
SAE, CVA	-	-	-	2 (<1)	-
SAE, Hemorrhagic stroke	-	-	-	2 (<1)	-
Baseline vs. Post-Baseline					
Systolic BP*					
Baseline mean	125	125	124	125	126
Post-baseline mean**	124	123	123	125	126
Diastolic BP*					
Baseline mean	76	77	76	76	77
Post-baseline mean**	76	76	76	77	78

* Blood pressure taken semi-supine (mmHg)
** Post baseline values are last post-baseline observation per patient
Escape data are excluded
Adapted from Tables 24, 50, 51, stae11_ir, and stae11-1 of Module 2.7.4

7.4.4 Electrocardiograms (ECGs)

Because of cardiac conduction abnormalities observed in a Castleman's Disease clinical trial, the approved Japanese label for tocilizumab contains a precaution about cardiac abnormalities and a recommendation that ECG testing should be conducted periodically. Therapeutic biologics, such as tocilizumab, are macromolecules with specific targets that are not considered likely to be able to affect the cardiac conduction system.

Nonetheless, to explore the issue further, the applicant has conducted a 2-part QT study, BP19461. This study is a single-center, randomized double-blind, placebo-controlled (6:2, active:placebo) study in 36 healthy volunteers who were given a single dose of TCZ at 2, 10, 20, or 28 mg/kg IV vs. placebo. ECG recordings were taken at baseline, then 2 hours after the start of infusion and weekly thereafter until Day 29. An ECG was also performed at the final follow-up visit on Day 50. All mean QTc values were ≤450 ms within 28 days for all subjects, except for the day 8 (QTcF 455 ms) and day 29 (QTcF 454 ms) values for one female subject who had received TCZ 20 mg/kg. No significant change from baseline in QTc were noted with the exception of a single male who had received placebo and had a change in QTcF of 32 ms on day 15. The final study report for the 2nd part of the study, which includes a more thorough QT evaluation of single doses of 10 mg/kg and 20 mg/kg, is pending review.

In the Roche pivotal RA studies, very few patients experienced changes in QT interval to a degree that might be cause for concern. As summarized in Table 37 below, the number of patients having a QTc value >500 ms was very low in all treatment groups. Patients experiencing changes in QT value >30 ms were more frequent, and the proportion of patients was highest in the TCZ 8 mg/kg treatment groups (27 to 32%) but was similarly elevated in the MTX monotherapy group. Changes in QT of greater magnitude, i.e. >60 ms, were much lower in incidence overall, and similar between the treatment groups in the range of 4-7%. However, within that range, incidence was highest in the TCZ treatment groups. Very few patients experienced the more clinically concerning scenario of QT >500 ms with >30 or 60 ms changes from baseline.

The safety database was explored for reported events that could possibly be related to QT prolongation, and these are also summarized in Table 37. No episodes of Torsade de pointes or sudden death were reported. A single case of ventricular fibrillation was reported in a placebo + DMARD treated patient. A single case of QT prolongation was reported as an adverse event in a patient on TCZ 8 mg/kg monotherapy but was not associated with a clinical adverse event.

Overall, changes in QT of a magnitude that could be clinically concerning were infrequent, and occurred in the control groups at similar rates. Given the range of variability in QT likely observed in this population, these data do not clearly implicate an additional risk attributable to TCZ treatment.

Table 37 Treatment-Emergent QT Abnormalities

Treatment-Emergent QT Abnormalities and Possibly Relevant Adverse Events in the Controlled Period of the Roche Pivotal RA Trials						
	6-months pooled safety population					
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ
Enrolled	1170	284	774	1582	288	2644
QT >500 ms	1 (<1)	-	1 (<1)	2 (<1)	1 (<1)	4 (<1)
QTc** >500 ms	8 (<1)	-	2 (<1)	8 (<1)	1 (<1)	11 (<1)
QT >500 ms or Δ >30ms	235 (20)	76 (27)	166 (22)	430 (27)	93 (32)	689 (26)
QT >500 ms or Δ >60ms	50 (4)	10 (4)	45 (6)	114 (7)	14 (5)	173 (7)
QT >500 ms and Δ >30ms	1 (<1)	-	-	2 (<1)	1 (<1)	3 (<1)
QT >500 ms and Δ >60ms	1 (<1)	-	-	1 (<1)	-	1 (<1)
Possibly relevant adverse events reported (preferred terms)						
Torsade de pointes	-	-	-	-	-	-
Arrhythmia	-	-	-	-	1 (<1)	1 (<1)
ECG QT prolonged	-	-	-	-	1 (<1)	1 (<1)
Sudden death	-	-	-	-	-	-
V-tach/V-fib	1 (<1)	-	-	-	-	-
Syncope	-	-	4 (<1)	3 (<1)	-	7 (<1)
Seizures	-	1 (<1)	-	2 (<1)	-	2 (<1)

*Includes MTX
**Fridericia's correction
Sources: STvs_qtabnorm, stae11_1 and stae11_s1 from Module 2.7.4

7.4.5 Special Safety Studies

No special safety studies were submitted with this BLA, with the exception of interim results of study BP 19461, intended as a QT evaluation, which is discussed in section 7.4.4 above.

7.4.6 Immunogenicity

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. 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. These results are summarized in Table 38, below.

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. 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.

Table 38 Immunogenicity Testing Results

Summary of Immunogenicity Testing Results							
	6 month 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[a]
Safety Population	1170	284	774	1582	288	2644	2439
Tested in Screening Assay	611	273	765	1513	275	2553	477
Tested after Escape	235	8	122	95	6	323/546[b]	n/a
Positive Screening/Confirmation Assays[c]	**6 (4 escape)**	**1**	**17**	**23**	**2**	**46 (4 escape)**	**13**
Positive neutralizing antibody	**2 (all escape)**	**0**	**8**	**19**	**1**	**30 (2 escape)**	**8**
Number of patients with event-driven testing	**47**	**8**	**59**	**83**	**17**	**159**	**75**
Pts with event-driven testing who tested pos.	**1 (escape)**	**0**	**4**	**4**	**1**	**10 (1 escape)**	**2**
positive screening/confirmation	*1 (escape)*	*0*	*4*	*3*	*1*	*9 (1 escape)*	*2*
positive neutralizing	*0*	*0*	*4*	*4*	*1*	*9*	*1*
Ab-pos. pts with events causing withdrawal	**1 (escape)**	**0**	**2**	**1**	**1**	**5 (1 escape)**	**0**
positive screening/confirmation	*1 (escape)*	*0*	*2*	*1*	*1*	*5 (1 escape)*	*0*
positive neutralizing	*0*	*0*	*2*	*1*	*1*	*4*	*0*
No.of Pts with Loss of Efficacy (LoE) testing	**28 (1 escape)**	**3**	**7**	**5**	**1**	**14 (1 escape)**	**50**
Ab-pos. pts withdrawing due to LoE	**0**	**0**	**0**	**0**	**0**	**0**	**1**
positive screening/confirmation	*0*	*0*	*0*	*0*	*0*	*0*	*1*
positive neutralizing	*0*	*0*	*0*	*0*	*0*	*0*	*1*

a) Only those patients who were not previously tested in the double-blind period are reported
b) includes 323 patients were tested after escaping from placebo/control to TCZ out of 546 total patients who escaped; includes 80 patients from placebo-controlled substudy of WA17824
c) Repeatedly positive or at last testing on study; only post-baseline positive results are counted
Source: BLA 125276 Amendment 18

Table 39 Infusion Reactions

Infusion Reactions in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment							
	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	2562
Pts with ≥1 Infusional AE**	60 (5)	13 (5)	59 (8)	109 (7)	25 (9)	193 (7)	274 (11)
Infusional DAEs	1 (<1)	-	3 (<1)	4 (<1)	1 (<1)	8 (<1)	2 (<1)
Selected AEs Occurring within 24 hours of Infusion:							
Hypertension	10 (1)	2 (1)	7 (1)	17 (1)	7 (2)	31 (1)	61 (2)
Hypotension	6 (1)	1 (<1)	3 (<1)	3 (<1)	1 (<1)	7 (<1)	15 (1)
Rash	3 (<1)	-	9 (1)	12 (1)	2 (1)	22 (1)	26 (1)
Urticaria	-	-	2 (<1)	2 (<1)	-	4 (<1)	7 (<1)
Angioedema	-	-	-	-	-	-	1 (<1)
Anaphylaxis	-	-	3 (<1)	3 (<1)	-	6 (<1)	2 (<1)
Hypersensitivity	-	-	1 (<1)	2 (<1)	-	3 (<1)	-
Infusion related reaction	-	-	2 (<1)	4 (<1)	1 (<1)	7 (<1)	7 (<1)

*Includes MTX
**Includes terms defined in Stae_gloss_ir of 120 day safety update
Sources: BLA Amendment 18 and rhstae11_ir and stae11_ir of 120 day safety update

As shown in Table 38, a small percentage (6%) of patients experiencing adverse events of potentially immunogenic origin tested positive for anti-TCZ antibodies. The majority of patients experiencing acute infusion reactions (Table 39, above) were therefore negative. A higher proportion (7-9% vs 5% in the placebo or MTX groups) of patients in the TCZ treatment groups experienced acute (within 24 hours) infusional adverse events, and the proportion did increase during the long-term extensions. However, the majority of these patients were able to continue treatment and did not experience recurrence. Of note, a total of 6 patients experienced anaphylactic reactions, all of which resulted in

withdrawal; 3 were positive for anti-TCZ antibodies, 1 was negative, and 2 were not tested. Anaphylactic reactions tended to occur after the second to fourth infusions.

Overall, immunogenicity and acute infusional adverse events occurred in a small fraction of patients who received TCZ treatment and did not appear to significantly impact the overall efficacy or safety profile of TCZ treatment. The frequency and severity of these events appear to be consistent with those observed with currently approved biologic treatments for RA.

Table 40 ANA and Autoimmune AE

ANA and Autoimmune AE in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment							
	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**
Baseline positive ANA	532 (45)	150 (53)	347 (45)	777 (49)	156 (54)	1280 (48)	994 (41)
Δ from pos to neg at wk 24	88 (8)	20 (7)	61 (8)	188 (12)	35 (12)	284 (11)	n.r.
Δ from neg to pos at wk 24	99 (8)	19 (7)	69 (9)	91 (6)	8 (3)	168 (6)	150 (6)
ANA pos pts with autoimmune AE:							
Cutaneous lupus	-	-	-	-	-	-	3
SLE	-	-	-	-	1	1	-
Psoriasis	3	-	-	-	1	1	1
Vitiligo	-	-	-	1	-	1	1
Autoimmune thyroiditis	-	-	1	1	-	2	1
Sicca syndrome	-	-	1	2	1	4	3
Sjogren's	-	2	1	-	-	1	1
Antiphospholipid syndrome	-	-	-	1	-	1	-

*Includes MTX
** 2562 enrolled at time of 120 day safety update, data presented are from original submission data cut off
ANA titers ≥1:80 are positive n.r. = not reported
Sources: Stana_neg2pos of Module 2.7.4, stae11_ai of WA18695/18696 CSR and section 3.9.9 of 120 day safety update

Almost half of enrolled patients in each treatment group had positive ANA titers (≥1:80) at baseline. Over the course of 24 weeks, a small proportion of patients seroconverted from positive to negative and from negative to positive, as summarized in Table 40 above. A similar proportion seroconverted from positive to negative and from negative to positive in the control groups and the TCZ 4 mg/kg treatment group; a higher proportion of patients seroconverted to negative in the TCZ 8 mg/kg treatment groups. This pattern suggests that TCZ treatment is not associated with an additional risk of ANA seropositivity.

Sporadic occurrence of other autoimmune disorders was observed in ANA positive patients, as summarized in Table 40 above. The pattern of occurrence of these AEs suggests a randomness that is more likely associated with inherent patient variability rather than TCZ treatment.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

The integrated safety results were displayed by treatment group, above, allowing for examination of potential differences in the safety profiles of TCZ 4 mg/kg vs. TCZ 8 mg/kg as add-on therapy. With respect to deaths, malignancies, and serious adverse events, these two treatment groups were similar. Exposure-adjusted incidence of serious infections appeared to be slightly lower with TCZ 4 mg/kg (4.7 per 100 pt-yrs) than with TCZ 8 mg/kg (5.7 per 100 pt-yrs, in combination with DMARDs).

Heavier patients received higher total doses due to the weight-based dosing regimen. As mentioned in section 6.1.9, heavier patients had somewhat higher exposures. The effect of higher total doses was explored indirectly via quantification of AE by body weight categories. As shown in Table 41 below, the proportion of patients experiencing any AE or infection was highest in the highest weight category regardless of treatment. In terms of SAE and SIE, the heaviest patients in the TCZ 8 mg/kg treatment groups did have the highest incidence, however, overall, the proportions in these groups were not consistently very different than those observed in the other treatment arms. Thus treatment with higher total doses of TCZ does not appear to pose an excessive additional risk for adverse events.

Table 41 Overview of Adverse Events by Weight Categories

Overview of Adverse Events by Weight in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment						
	6-months pooled safety population					Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	Pooled TCZ
Enrolled	1170	284	774	1582	288	2439**
Number of patients						
>100 kg	105	28	60	122	22	215
≥60 to ≤100 kg	776	181	525	1076	200	1646
<60 kg	285	74	185	378	63	578
missing	4	1	4	6	3	-
Adverse events expressed as percentage of patients within weight category:						
Any AE						
>100 kg	76 (72)	19 (68)	51 (85)	96 (79)	19 (86)	191 (89)
≥60 to ≤100 kg	482 (62)	136 (75)	370 (70)	780 (72)	153 (76)	1366 (83)
<60 kg	173 (61)	64 (86)	123 (66)	254 (67)	55 (87)	481 (83)
Any infection						
>100 kg	43 (41)	10 (36)	30 (50)	57 (47)	9 (41)	144 (67)
≥60 to ≤100 kg	241 (31)	62 (34)	179 (34)	390 (36)	65 (32)	870 (53)
<60 kg	90 (32)	34 (46)	60 (32)	143 (38)	24 (38)	308 (53)
SAE						
>100 kg	4 (4)	1 (4)	2 (3)	8 (7)	1 (5)	29 (13)
≥60 to ≤100 kg	46 (6)	6 (3)	30 (6)	70 (6)	9 (4)	206 (13)
<60 kg	12 (4)	1 (1)	14 (8)	16 (4)	1 (2)	46 (8)
SIE						
>100 kg	-	1 (4)	1 (2)	5 (4)	1 (5)	14 (7)
≥60 to ≤100 kg	13 (2)	1 (1)	7 (1)	28 (3)	2 (1)	64 (4)
<60 kg	4 (1)	-	5 (3)	5 (1)	1 (2)	15 (3)
AE leading to Discontinuation						
>100 kg	1 (1)	2 (7)	2 (3)	6 (5)	-	10 (5)
≥60 to ≤100 kg	17 (2)	10 (6)	23 (4)	52 (5)	8 (4)	85 (5)
<60 kg	10 (4)	3 (4)	12 (6)	15 (4)	3 (5)	21 (4)

*Includes MTX

** 2562 enrolled at time of 120 day safety update, data presented are from original submission data cut off

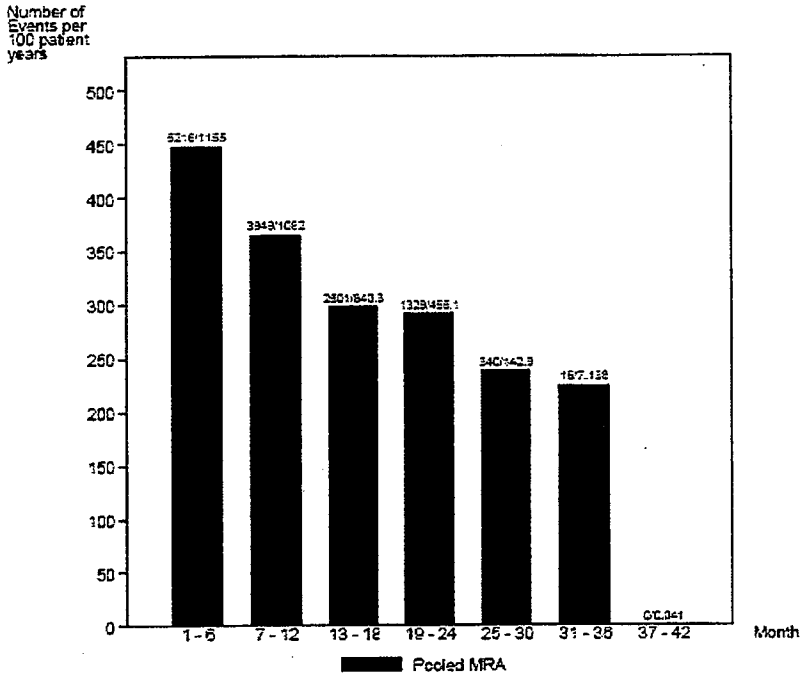
Sources: Table 56 of Module 2.7.4, stae11_wgt, stae11_wgt_s, stae11_wgt_wd, and stae11_wgtinf_s of WA18695/18696 CSR

7.5.2 Time Dependency for Adverse Findings

As noted in Table 18 above, the exposure-adjusted incidence of death, malignancy, serious adverse events and serious infections did not increase in the long-term extension. This is confirmed by an additional analysis assessing the rate of adverse events by 6-month periods for patient in the long-term extension. Figure 16 below shows that the exposure-adjusted rate of adverse events was highest in the initial 6-month period of the trials and fell with successive 6-month intervals.

Figure 16: Rate of Adverse Events by 6-Month Periods

SGrate_ae_6m Rate of Adverse Events by 6-Monthly Periods (Safety Population)



The numbers above the bars represent the number of AEs over the number of years exposure.
Month is equivalent to 28 days
Multiple occurrences of events per patient per interval are counted only once

Source: Figure 1 of the 120 day safety update

7.5.3 Drug-Demographic Interactions (gender, race)

Adverse events by body weight categories are discussed in section 7.5.1. above. Adverse events by age, gender, and race are summarized below in Table 42, Table 43, and Table 44, respectively.

Very few patients were ≥75 years old, making comparison of the data in this age category difficult. However, taking into account the other age categories, there were no consistent trends toward increased incidence of AE with increasing age.

Table 42 Adverse Events by Age

Overview of Adverse Events by Age in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment						
	6-months pooled safety population					Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	Pooled TCZ
Enrolled	1170	284	774	1582	288	2439**
Number of patients						
>75 years	29	6	10	35	5	50
≥65 to ≤75 years	170	30	113	237	35	325
≥50 to 64 years	520	113	316	765	121	1122
<50 years	451	135	335	545	127	942
Adverse events expressed as percentage of patients within age category:						
Any AE						
>75 years	23 (79)	5 (83)	8 (80)	26 (74)	3 (60)	42 (84)
≥65 to ≤75 years	108 (64)	19 (63)	82 (73)	171 (72)	22 (77)	276 (85)
≥50 to 64 years	327 (63)	90 (80)	231 (73)	557 (73)	100 (83)	932 (83)
<50 years	275 (61)	106 (79)	226 (67)	380 (70)	100 (79)	788 (84)
Any infection						
>75 years	12 (41)	4 (67)	3 (30)	11 (31)	1 (20)	27 (54)
≥65 to ≤75 years	52 (31)	8 (27)	50 (44)	83 (35)	14 (40)	181 (56)
≥50 to 64 years	158 (30)	40 (35)	112 (35)	300 (39)	38 (31)	617 (55)
<50 years	152 (34)	54 (40)	105 (31)	198 (36)	46 (36)	497 (53)
SAE						
>75 years	4 (14)	1 (2)	1 (10)	4 (11)	2 (40)	11 (22)
≥65 to ≤75 years	13 (8)	1 (3)	13 (12)	24 (10)	1 (3)	62 (19)
≥50 to 64 years	27 (5)	4 (4)	21 (7)	51 (7)	5 (4)	138 (12)
<50 years	18 (4)	2 (1)	11 (3)	16 (3)	3 (2)	70 (7)
SIE						
>75 years	1 (3)	1 (17)	1 (10)	-	-	3 (6)
≥65 to ≤75 years	4 (2)	-	5 (4)	9 (4)	1 (3)	22 (7)
≥50 to 64 years	9 (2)	1 (1)	5 (2)	23 (3)	2 (2)	45 (4)
<50 years	3 (1)	-	2 (1)	6 (1)	1 (1)	23 (2)
AE leading to Discontinuation						
>75 years	1 (3)	-	1 (10)	2 (6)	2 (40)	5 (10)
≥65 to ≤75 years	10 (6)	1 (3)	6 (5)	13 (5)	2 (6)	15 (5)
≥50 to 64 years	8 (2)	9 (8)	14 (4)	37 (5)	3 (2)	59 (5)
<50 years	9 (2)	5 (4)	17 (5)	22 (4)	4 (3)	37 (4)

*Includes MTX

** 2562 enrolled at time of 120 day safety update, data presented are from original submission data cut off

Sources: Table 53 of Module 2.7.4, stae11_age, stae11_age_s, stae11_age_wd, and stae11_ageinf_s of WA18695/18696 CSR

In terms of trends by gender categories, a lower proportion of males experienced any AE and any infection in the TCZ 8 mg/kg treatment groups, however this trend is not consistent among other AEs, to include serious infections. Overall the data do not suggest significant differences in safety between the genders.

Table 43: Adverse Events by Gender

Overview of Adverse Events by Gender in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment						
	6-months pooled safety population					Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	Pooled TCZ
Enrolled	1170	284	774	1582	288	2439**
Number of patients						
Male	210	60	133	282	50	444
Female	960	224	641	1300	238	1995
Adverse events expressed as percentage of patients within gender category:						
Any AE						
Male	131 (62)	46 (77)	90 (68)	189 (67)	35 (70)	365 (82)
Female	602 (63)	174 (78)	457 (71)	945 (73)	195 (82)	1673 (84)
Any infection						
Male	56 (27)	18 (30)	46 (35)	87 (31)	13 (26)	220 (50)
Female	318 (33)	88 (39)	224 (35)	505 (39)	86 (36)	1102 (55)
SAE						
Male	16 (8)	5 (8)	6 (5)	14 (5)	2 (4)	60 (14)
Female	46 (5)	3 (1)	40 (6)	76 (6)	10 (4)	221 (11)
SIE						
Male	3 (1)	2 (3)	2 (2)	8 (3)	-	17 (4)
Female	14 (1)	-	11 (2)	30 (2)	4 (2)	76 (4)
AE leading to Discontinuation						
Male	5 (2)	5 (8)	6 (5)	14 (5)	2 (4)	23 (5)
Female	23 (2)	10 (4)	32 (5)	60 (5)	9 (4)	93 (5)

*Includes MTX

** 2562 enrolled at time of 120 day safety update, data presented are from original submission data cut off

Sources: Table 54 of Module 2.7.4, stae11_gen, stae11_gen_s, and stae11_gen_wd of WA18695/18696 CSR

Caucasians comprised between 70-75% of the study population in each treatment group. Black patients were the least common, comprising 4-8% of the study population in each treatment group. Since non-Caucasian racial subgroups were small, definitive conclusions cannot be made regarding propensity toward adverse events; however, no consistent trends were observed.

Table 44 Adverse Events by Race

Overview of Adverse Events by Race in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment						
	6-months pooled safety population					Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	Pooled TCZ
Enrolled	1170	284	774	1582	288	2439**
Number of patients						
White	875	207	584	1165	203	1841
Asian	90	21	46	132	24	222
Native American	72	22	43	117	29	203
Black	47	13	34	67	12	91
Other	86	21	67	101	20	82
Adverse events expressed as percentage of patients within racial category:						
Any AE						
White	554 (63)	161 (78)	413 (71)	825 (71)	155 (75)	1519 (83)
Asian	45 (50)	19 (90)	36 (78)	94 (71)	23 (96)	189 (85)
Native American	50 (69)	18 (82)	32 (74)	91 (78)	26 (90)	182 (90)
Black	32 (68)	6 (46)	23 (68)	50 (75)	11 (92)	72 (79)
Other	52 (60)	16 (76)	43 (64)	74 (73)	17 (85)	76 (93)
Any infection						
White	270 (31)	77 (37)	210 (36)	429 (37)	52 (26)	991 (54)
Asian	25 (28)	9 (43)	13 (28)	39 (30)	17 (71)	111 (50)
Native American	33 (46)	9 (41)	18 (42)	52 (44)	13 (45)	126 (62)
Black	12 (26)	2 (15)	10 (29)	26 (39)	5 (42)	46 (51)
Other	28 (33)	9 (43)	15 (22)	39 (39)	9 (45)	48 (59)
SAE						
White	52 (6)	6 (3)	40 (7)	80 (7)	10 (5)	228 (12)
Asian	-	1 (5)	1 (2)	4 (3)	1 (4)	10 (5)
Native American	5 (7)	-	1 (2)	6 (5)	-	25 (12)
Black	1 (2)	-	1 (3)	1 (1)	-	9 (10)
Other	4 (5)	1 (5)	3 (4)	4 (4)	-	9 (11)
SIE						
White	13 (1)	2 (1)	12 (2)	29 (2)	3 (1)	72 (4)
Asian	-	-	1 (2)	3 (2)	1 (4)	3 (1)
Native American	2 (3)	-	-	4 (3)	-	14 (7)
Black	-	-	-	-	-	2 (2)
Other	2 (2)	-	-	2 (2)	-	2 (2)
AE leading to Discontinuation						
White	22 (3)	11 (5)	31 (5)	56 (5)	7 (3)	89 (5)
Asian	1 (1)	3 (14)	1 (2)	5 (4)	2 (8)	6 (3)
Native American	4 (6)	-	1 (2)	6 (5)	1 (3)	15 (7)
Black	-	-	1 (3)	5 (7)	1 (8)	4 (4)
Other	1 (1)	-	4 (6)	2 (2)	-	2 (2)

*Includes MTX

** 2562 enrolled at time of 120 day safety update, data presented are from original submission data cut off

Sources: Table 53 of Module 2.7.4, stae11_race, stae11_race_s, and stae11_race_wd of WA18695/18696 CSR

7.5.4 Drug Disease Interactions

No specific drug-disease interactions have been noted in the global TCZ development program in RA and other indications.

7.5.5 Drug-Drug Interactions

See section 4.4 Clinical Pharmacology.

7.6 Additional Safety Evaluations

Safety evaluations have been covered in the other subsections of section 7.

7.6.1 Human Carcinogenicity

See section 7.3 for a discussion of neoplasms and malignancies in the pivotal trials.

7.6.2 Human Reproduction and Pregnancy Data

As of the data cut-off for the 120 day safety update, a total of 23 patients became pregnant during their participation in the Roche clinical trials for TCZ. Of these 23 patients, the outcome is known for 18 and five are currently ongoing. In the 18 pregnancies where the outcome is known, 11 had induced abortions, six had spontaneous abortions and one had a normal newborn. Fourteen patients received TCZ + MTX, four patients in study WA17823 received blinded TCZ + MTX, and five patients received MTX monotherapy. The patient with a normal newborn did not receive MTX during the trial and stopped treatment with TCZ after the pregnancy was diagnosed.

All, except one patient, reported using contraceptive methods at the time that pregnancy occurred as mandated by the study protocols. Currently there are five reports of ongoing pregnancies. TCZ and/or MTX have been discontinued in all but one case where termination is planned.

This small cohort of patients, whose exposure was also confounded by potentially deleterious agents such as methotrexate, is not sufficient to draw definitive conclusions about the possible effect of TCZ on human reproduction and pregnancy.

7.6.3 Pediatrics and Assessment and/or Effects on Growth

This submission for the adult RA indication invokes a requirement for a pediatric assessment in polyarticular juvenile idiopathic arthritis (PJIA) patients, as per the Pediatric Research Equity Act (PREA). In this submission, the applicant has provided a

request for deferral of studies in PJIA patients 2-17, and a waiver for the 0-2 year old age group, given that JIA is extremely rare in very young children. The applicant has already conducted trials in pediatric patients with PJIA and systemic JIA in Japan, and was recently (April 2008) approved for these indications there.

The applicant met with the Division in March 2007 to discuss their plans for pediatric studies in PJIA and SJIA, and came to agreement in December 2007 on a special protocol assessment (SPA) for the proposed SJIA study. They submitted a protocol for PJIA earlier this year taking into account the advice provided by the Division in March 2007, and based on dose-response information from the adult RA studies, with an expectation that this study would begin enrolling in the 4th quarter of 2008.

Table 45 Overview of JIA studies

Overview of Completed and Ongoing Juvenile Idiopathic Arthritis Studies (SJIA and PJIA)						
Study	Design	Dose/Regimen	Duration	# Patients	Major Efficacy	Major Safety
SJIA						
MRA316JP Japan	RDBPCT withdrawal	8 mg/kg q 2 wks x 3 in open phase 8 mg/kg vs pbo q 2 wks x 6	6 wks open, 12 wk withdrawal	56 dosed 10 withdrawn ages 2-19	Open: 86% JIA 30 Withdrawal: 20% flare TCZ 84% flare PBO	2 SAE Infectious all recovered
MRA317JP Japan	open-label LTE	8 mg/kg q 2 wks	> 2 yrs	60 dosed 2 withdrawn		2 DAE (1 anaphylaxis)
MRA011JP Japan	open-label	2 mg/kg q 2 wks x 3, then dose individualized to normalize CRP 4 or 8 mg/kg q 2 wks	6-14 wks > 1 yr extension	11 dosed 1 withdrawn ages 3-18	91% JIA30 and JIA 50	10 SAE in 7 pts Infectious all recovered
LRO320 EU	open-label	single dose of 2, 4, or 8 mg/kg		18 dosed 0 withdrawn ages 2-17		5 SAE Disease flare Infectious
MRA324JP Japan	open-label expanded access	8 mg/kg q 2 wks up to weekly	until marketed	32 dosed 0 withdrawn ages 2-25		2 cases of MAS
PJIA						
MRA318JP Japan	open-label	8 mg/kg q 4 wks	12 wks	19 dosed 0 withdrawn	90-95% JIA30 53-58% JIA50	URI, nasopharyngitis, gastroenteritis
MRA319JP	open-label LTE	8 mg/kg q 4 wks	> 1 yr	19 dosed 1 withdrawn		

Source: IND 11972 February 12, 2007 pediatric EOP2 meeting package

Table 45 above summarizes the tocilizumab foreign JIA studies performed thus far. Overall, results suggest tocilizumab may be highly effective in the treatment of JIA. Treatment with tocilizumab also allowed for greater reductions in concomitant steroid usage (data not shown). The adverse event profile from these studies is similar to that observed in adult RA studies; infections were common and treatment-related changes in laboratory parameters were also noted.

7.6.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

One case of accidental overdose was reported in which a patient with multiple myeloma received a dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg/kg, although all 5 patients at the highest dose of 28 mg/kg developed dose-limiting neutropenia. TCZ is of low abuse potential as it is a macromolecule that should not cross the blood-brain barrier and IL6 is not known to have CNS mood or mind-altering effects. As monoclonal antibodies have extended half-lives and relatively slow clearance, withdrawal and rebound phenomenon are not expected and have not been observed in patients who have missed doses in the clinical development program.

7.7 Additional Submissions

Information from amendments to the original BLA submission has been incorporated into the applicable safety sections of this review.

8. POSTMARKETING EXPERIENCE

Tocilizumab has been marketed in Japan since April 2005 for the rare condition of multicentric Castleman's Disease. As of January 2008, 171 patients have been treated for a total exposure of 246 patient-years. The observed safety profile in Castleman's Disease trials is similar to that observed in the RA trials, although rash occurred more frequently, in 17 of 36 (49%) of patients. Postmarketing data from this and the more recently approved (April 2008) indications are not available for review.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

Dixon WG et al., "Serious Infection Following Anti-Tumor Necrosis Factor Therapy in Patients with Rheumatoid Arthritis." Arthritis & Rheum, September 2007, 56(9):2896-2904.

Doran MF, et al., "Frequency of Infection in Patients with Rheumatoid Arthritis Compared with Controls: a Population Based Study." Arthritis & Rheum, September 2002, 46(9):2287-2293.

Gonzalez A, et al., "The Widening Mortality Gap Between Rheumatoid Arthritis Patients and the General Population." Arthritis & Rheum, November 2007, 56(11):3583-3587.

Hewlett S, et al., "Measuring Fatigue in Rheumatoid Arthritis: A Systematic Review of Scales in Use." Arthritis & Rheum, April 15 2007, 57(3):429-439.

Listing J, et al., "Infections in patients with rheumatoid arthritis treated with biologic agents." Arthritis & Rheum, November 2005, 52(11):3403-3412.

Mellemkjaer L, et al., "Rheumatoid Arthritis and Cancer Risk." Eur J Cancer, September 1996, 32A(10):1753-7.

Naugler WE, and M Karin, "The Wolf in Sheep's Clothing: the Role of Interleukin-6 in Immunity, Inflammation, and Cancer." Trends in Molecular Medicine 14(3):109-119.

Wolfe F, and DJ Hawley, "The Comparative Risk and Predictors of Adverse Gastrointestinal Events in Rheumatoid Arthritis and Osteoarthritis: a Prospective 13 Year Study of 2131 Patients." J Rheumatol, July 2000, 27(7):1668-73.

Wolfe F, and K Michaud, "Biologic Treatment of Rheumatoid Arthritis and the Risk of Malignancy." Arthritis & Rheum, September 2007, 56(9):2886-2895

9.2 Labeling Recommendations

Trade Name:

The proposed trade name for tocilizumab, Actemra, has been reviewed by the Division of Medication Errors and Technical Support (DMETS) and was determined to be acceptable.

Patient Package Insert vs. Medication Guide:

As per 21 CFR 208, a medication guide is required if the patient labeling could help prevent serious adverse effects, the product has significant risks relative to benefits that could affect the patient's use of the product, or if the patient must adhere to the directions for use in order for the drug to be effective.

The primary risks of TCZ treatment that have been demonstrated in the clinical experience to date include an increased risk of serious infections, and TCZ-related changes in laboratory parameters. Patients should be informed about possible toxicities, e.g. serious infections, so they can obtain medical attention promptly if they occur. Because TCZ is administered by IV infusion, the patient will not be using the product in an unsupervised setting, and infusion visits will provide opportunity to obtain laboratory tests when necessary. However, in view of the toxicities that have been observed in the clinical development program, a medication guide is warranted.

The applicant submitted a proposed patient package insert (PPI), but will be advised that they must submit a MedGuide.

Suggested Revisions to Proposed Labeling:

Dosing Regimen and Administration

The proposed recommended dosing regimen is 8 mg/kg given once every 4 weeks as a 60-minute single intravenous drip infusion, as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs. The applicant has proposed scenarios for dose-modification (i.e. to 4 mg/kg) or dose-interruption that mirror protocol scenarios. Since these scenarios are straightforward and limited in number, and appeared to be effective in the clinical trials to avoid clinical consequences of abnormalities in laboratory parameters, these instructions are appropriate for inclusion in the PI.

The proposed PI contains section 2.3 for dosage modifications as follows:

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

b(4)

Labeling Pertaining to Efficacy
I recommend the following major efficacy-related revisions:

b(4)

9.3 Advisory Committee Meeting

An advisory committee meeting was scheduled to be convened for this application on July 29, 2008. The Arthritis Advisory Committee will be asked to deliberate on:

1. The safety of tocilizumab, with special attention to serious infections, liver enzyme abnormalities, lipid parameter changes, gastrointestinal perforations, and demyelinating disorders and the implications of these with respect to the need for monitoring or selection of appropriate patients for treatment;
2. Appropriate dosing, and whether there are patients at higher risk of adverse events for whom a lower dose should be recommended (i.e., 4 mg/kg instead of 8 mg/kg);
3. In view of the data available for safety and efficacy, whether the committee would recommend approval of tocilizumab for the treatment of patients with moderately to severely active rheumatoid arthritis; and
4. If the committee recommends approval, they were asked what additional post-marketing studies they would recommend in addition to the ongoing 5-year long-term extension studies and the typically requested immunization response studies. If the committee recommends against approval, they were asked what additional data would be needed to gain approval.

9.4 Individual Study Reports

9.4.1 Study WA17822

9.4.1.1 WA17822 Study Protocol

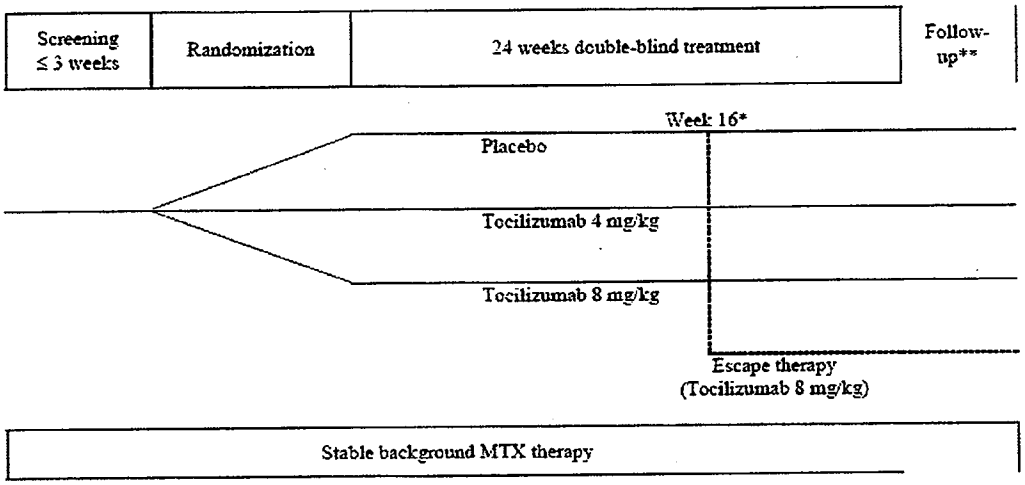
Overall Study Design

Study WA17822 is a 24-week randomized, double-blind, placebo-controlled study in 623 patients with moderately to severely active RA with previous inadequate clinical response to MTX at a dose of at least 10-25 mg per week. This study was conducted entirely outside the US, at 73 centers in 17 countries worldwide. The WA17822 study schema is depicted in Figure A-17 below.

Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks, given in addition to background treatment with MTX 10 to 25 mg (stable dose) weekly. Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy (TCZ 8 mg/kg + MTX) at weeks 16 and 20.

The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the week 24 visit, all patients (including escape patients) could roll-over into an open-label long-term extension study (WA18695) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years.

Figure A-17, WA17822 Study Schema



*Patients who did not achieve a 20% improvement from baseline in both SJC and TJC at week 16 could receive escape therapy (comprising tocilizumab 8 mg/kg + MTX) at weeks 16 and 20.
**Patients who did not enroll into long-term extension study WA18695 returned for safety follow-up assessments 8 and 12 weeks after the last infusion of study treatment.
Figure 1 of WA17822 CSR

Inclusion Criteria

1. Able and willing to give written informed consent and comply with the requirements of the study protocol
2. Patients with RA of ≥ 6 months duration, diagnosed according to the revised 1987 American College of Rheumatology
3. Receiving treatment on an outpatient basis
4. Prior to randomization, had discontinued etanercept for ≥ 2 weeks, infliximab or adalimumab for ≥ 8 weeks, anakinra for ≥ 1 week, leflunomide for ≥ 12 weeks (or ≥ 4 weeks after 11 days of standard cholestyramine washout)
5. Had received MTX for at least 12 weeks immediately prior to baseline, of which the last 8 weeks prior to baseline had been at a stable dose of between 10 and 25 mg/week (oral or parenteral)
6. All DMARDs, other than MTX, withdrawn prior to baseline
7. SJC ≥ 6 (66 joint count) and TJC ≥ 8 (68 joint count) at screening and baseline
8. At screening, C-reactive protein (CRP) ≥ 1 mg/dL (10 mg/L) or erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour
9. Age ≥ 18 years
10. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if the dose was stable for at least 6 weeks prior to baseline

11. Females of child-bearing potential and males with female partners of child-bearing potential could participate in this trial only if using a reliable means of contraception (e.g., physical barrier [patient and partner], contraceptive pill or patch, spermicide and barrier, or IUD)
12. Willing to receive oral folate
13. If female and of childbearing potential, the patient must have had a negative urine pregnancy test within 3 weeks prior to baseline.

Exclusion Criteria

General:

1. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization
2. Rheumatic autoimmune disease other than RA, including SLE, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to RA (eg, vasculitis, pulmonary fibrosis or Felty's syndrome). Secondary Sjögren's syndrome with RA was permitted
3. Functional class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis
4. History of, or current, inflammatory joint disease other than RA (eg, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease).

Excluded Previous or Concomitant Therapy:

5. Unsuccessful treatment with an anti-TNF agent (ie, significant safety issues or lack of efficacy. Patients who terminated previous anti-TNF treatment due to cost or discomfort with the subcutaneous injections could participate in this study)
6. Treatment with any investigational agent within 4 weeks (or five half-lives of the investigational drug, whichever was longer) of screening
7. Previous treatment with any cell-depleting therapies, including investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19 and anti-CD20)
8. Treatment with intravenous gamma globulin, plasmapheresis or Prosorba™ column within 6 months of baseline
9. Intra-articular or parenteral corticosteroids within 6 weeks prior to baseline
10. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline
11. Previous treatment with tocilizumab (an exception to this criterion could be granted for single dose exposure upon application to the applicant on a case-by-case basis)
12. Any previous treatment with alkylating agents such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.

Exclusions for General Safety:

13. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies

14. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or gastrointestinal disease
15. Uncontrolled disease states, such as asthma, psoriasis or inflammatory bowel disease, for which flares are commonly treated with oral or parenteral corticosteroids
16. Current liver disease as determined by the principal investigator. (Patients with prior history of alanine aminotransferase [ALT] elevation were not excluded)
17. History of, or known currently active, recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest radiograph as determined by the investigator, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening
18. Primary or secondary immunodeficiency (history of or currently active)
19. Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including hematological malignancies and solid tumors, except basal cell carcinoma of the skin that has been excised and cured), or breast cancer diagnosed within the previous 20 years
20. Pregnant women or nursing (breast feeding) mothers
21. History of alcohol, drug or chemical abuse within 6 months prior to screening
22. Neuropathies or other painful conditions that might interfere with pain evaluation
23. Patients with lack of peripheral venous access
24. Body weight > 150 kg.

<u>Laboratory Exclusion Criteria (at Screening):</u>

25. Serum creatinine > 124 μmol/L (1.4 mg/dL) for female patients and > 141 μmol/L (1.6 mg/dL) for male patients
26. ALT or aspartate aminotransferase (AST) > 1.5 times the upper limit of normal (ULN). (If the initial sample yielded ALT or AST > 1.5x ULN, a second sample could be taken and tested during the screening period)
27. Platelet count < 100 x 10^9/L (100000/mm3)
28. Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
29. White blood cells (WBC) < 3 x 10^9/L (3000/mm3)
30. Absolute neutrophil count < 2 x 10^9/L (2000/mm3)
31. Absolute lymphocyte count < 0.5 x 10^9/L (500/mm3)
32. Positive hepatitis B surface antigen (HbsAg) or hepatitis C antibody
33. Total bilirubin > ULN. (If the initial sample yielded bilirubin > ULN, a second sample could be taken and tested during the screening period)
34. Triglycerides > 10 mmol/L (> 900 mg/dL) at screening (non-fasted).

Concomitant Medications

In addition to tocilizumab, all patients received MTX at a stable pre-entry dose of between 10 and 25 mg/week. Patients eligible for the study had received MTX for at least 12 weeks immediately prior to randomization, and at a stable dose for the last 8 weeks prior to baseline. The dose and route of administration of MTX at entry into the study was to be continued without change while the patient was on double-blind therapy (i.e., for 24 weeks). Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted during the study if the dose had been stable for at least 6 weeks prior to baseline. Immunization with a live or attenuated vaccine was prohibited within 4 weeks prior to the baseline visit and for the duration of study participation, including the 12-week follow-up period after administration of the last infusion of study treatment.

Methotrexate: Dose reductions of MTX or a change of route of administration could be made at any time for safety reasons.

NSAIDs: Patients could be treated with NSAIDs up to the maximum recommended dose, (including COX-2 inhibitors) throughout the study. An alteration in NSAID dose was strongly discouraged over the first 24 weeks of the study. Dose adjustments could be made for safety reasons and, if absolutely required, to treat disease flares. Aspirin (dose not exceeding 350 mg/day) could be taken to manage cardiovascular risk.

Oral corticosteroids: Alterations in background oral corticosteroid dose were strongly discouraged over the first 24 weeks of the study. To treat non-RA conditions such as asthma, increased doses of oral corticosteroids (up to 40 mg prednisone, or equivalent, daily for 2 weeks or less) were permitted. The corticosteroid dose was to be tapered down to the previous level as rapidly as medically possible.

Intravenous, intramuscular or intra-articular corticosteroids: Treatment with intravenous or intramuscular corticosteroids was not permitted during the study. Similarly, the use of intra-articular corticosteroids was not permitted within 6 weeks prior to baseline. Injection of intra-articular corticosteroids while on blinded study treatment was also discouraged, but was allowed to a limited extent. No more than one joint was to be injected and no single injection was to exceed 40 mg of triamcinolone (or equivalent). Injection of any joint at, or after, week 16 resulted in the patient being excluded from the efficacy analysis.

Analgesics (other than NSAIDs): Analgesics up to the maximum recommended doses could be used for pain as required. However, patients were discouraged from taking analgesics within 24 hours prior to a visit at which clinical efficacy assessments were performed and recorded.

Folic Acid: In order to minimize MTX toxicity, all patients received a stable dose of

≥ 5 mg/week folate (or equivalent) given, at the investigator's discretion, as either a single dose or as daily doses.

The use of DMARDs other than MTX or biologic DMARDs was prohibited throughout the study.

Assignment to treatment group

Approximately 630 patients were to be randomly assigned in an equal manner to one of three treatment groups: placebo + MTX, tocilizumab 4 mg/kg + MTX or tocilizumab 8 mg/kg + MTX.

Randomization was administered centrally via an interactive voice response system (IVRS) and was stratified by 'site' using a randomization list provided by Roche. A patient's eligibility was evaluated by the investigator to ensure that the inclusion and exclusion criteria were met and that the patient was eligible for participation in the study. Eligible patients were then randomized and assigned a unique randomization number. Medication numbers were assigned by the IVRS prior to dosing at each dosing visit depending on the patient's weight and allocated treatment arm in order to ensure that the correct dosage was provided.

Blinding

This was a blinded study, with the applicant, investigators, and patients unaware of the treatment assignment of each patient. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment.

In order to maintain the double-blind status of the study, once infused study treatment had commenced, acute phase reactant data from the central laboratory were blinded to site and applicant personnel. Results of the PK assays were also not available to the investigators and were blinded to the applicant and monitors during the course of the study.

Drug Administration

Tocilizumab or placebo was administered intravenously every 4 weeks on an outpatient basis. Tocilizumab was to be administered under close supervision of the investigator or subinvestigator, in a setting where resuscitation facilities were available.

Two, four or six vials of tocilizumab or placebo were assigned to each patient for each infusion according to the patient's bodyweight (ie, ≤ 50 kg, > 50 to ≤ 100 kg, or > 100 kg, respectively). The maximum weight dosed was 150 kg (ie, maximum 1200 mg dose).

Tocilizumab/placebo was administered at room temperature by controlled infusion into an arm vein over a one-hour period. The infusion speed of the 100 mL infusion bag was to be 10 mL/hour for 15 minutes and then increased to 130 mL/hour to complete the dosing over 1 hour. In exceptional circumstances, it was allowable for the infusion time to be extended for up to 6 hours.

Criteria for Withdrawal from Treatment or Study and Replacement Policy

Patients were free to withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violations, cure, administrative reasons or other reasons. Should a patient decide to withdraw, all efforts were to be made to complete and report the observations as thoroughly as possible. The reason for withdrawal was to be determined by the investigator or responsible person. If the reason for removal of a patient from the study was an adverse event or an abnormal laboratory test result, the principal specific event or test was also recorded on the adverse event case report form (CRF). Patients withdrawn from the study were not replaced.

Dose Modification

1. ALT or AST elevations:
   - Patients who experienced an increase in ALT or AST to ≥ 3x ULN were required to withhold the next infusion of study treatment. Blood samples were taken every 2 weeks thereafter. Once the patient's ALT and AST value had returned to < 3x ULN, study treatment could recommence at the next scheduled 4 weekly visit.
   - If the patient had a second ALT or AST elevation to ≥ 3x ULN on recommencing treatment, study treatment was to be permanently discontinued.
   - If a patient had an ALT or AST elevation to > 2x ULN but < 3x ULN, a blood sample was to be taken immediately prior to the next dose of tocilizumab to verify that the ALT or AST value had remained < 3x ULN.
   - If a patient had an ALT or AST elevation to > 5x ULN, study treatment was to be permanently discontinued.
   - If two consecutive doses of tocilizumab were missed due to ALT or AST elevations, study treatment was to be permanently discontinued.

2. Bilirubin elevations:
   - If a patient experienced a level of indirect bilirubin > 2x ULN or a total bilirubin value of > 43 μmol/L (2.5 mg/dL), study treatment was to be permanently discontinued.

3. Infections:

- Clinical signs which should warn the investigator of possible drug toxicity include severe infection or frequent minor infections, mucositis and pneumonitis. The investigator was to report such signs to the sponsor, provide appropriate treatment and discontinue study treatment if deemed necessary.

4. Absolute neutrophil count decreases:
   - If a patient's absolute neutrophil count decreased to $< 0.5 \times 10^9$/L (500/mm^3), study treatment was to be permanently discontinued.

The abnormal laboratory test values and infections referred to above were to be reported as adverse events.

Infusion Reactions

Infusion reactions were defined as any reaction occurring during the infusion of tocilizumab or corresponding placebo or within 24 hours following the infusion. Any such reaction was recorded as an adverse event on the CRF. If any signs of a possible infusion reaction (eg, fever, chills, pruritus, urticaria or cardiopulmonary reactions including chest pain, dyspnea, hypotension or hypertension) were observed during the infusion and the patient remained hemodynamically stable the infusion rate was to be slowed down (at least halved) and the infusion time extended. If the patient continued to display signs and symptoms of hypersensitivity, an intramuscular or slow intravenous dose of an antihistamine was to be administered. Patients who experienced a severe infusion-related reaction with cardiovascular compromise were to have their infusion discontinued and were to be treated for an anaphylactic reaction. No further study treatment was to be given and the patient was to be removed from the study.

Schedule of Assessments

Table A-46 Schedule of Assessments for Study WA17822

	Week (± 3 days)												
	-3* SC	0* BL	2	4	6	8	12	14	16	20	24 WD 1	28 WD 2	32 WD 3
Informed consent	x												
Demographics	x												
Medical history	x[1]	x											
Inclusion/exclusion	x	x											
Pregnancy test (urine)[2]	x	x		x		x	x		x	x	x		
Physical examination	x										x		
Vital signs, weight	x	x[3]		x[3]		x[3]	x[3]		x[3]	x[3]	x	x	x
Study drug infusion[4]		x		x		x	x		x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x[5]										x		
Chest radiograph	x												
Efficacy													
Joint counts	x	x	x	x		x	x		x	x	x		
PT/INV global		x	x	x		x	x		x	x	x		
Pain VAS		x	x	x		x	x		x	x	x		
HAQ-DI		x	x	x		x	x		x	x	x		
FACIT-Fatigue		x		x		x	x		x	x	x		
SF-36		x				x			x		x		
Medical resource utilization		x		x		x	x		x	x	x		
EQ-5D		x				x			x		x		
WPAI		x				x			x		x		
High sensitivity CRP	x	x	x	x	x	x	x	x	x	x	x		
ESR	x	x	x	x	x	x	x	x	x	x	x		
SAA[6]		x	x	x	x	x	x	x	x	x	x		
Serum ferritin[6]		x	x	x	x	x	x	x	x	x	x		
Haptoglobin[6]		x	x	x	x	x	x	x	x	x	x		
Safety													
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x
Hematology (CBC)	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood chemistry (including LFTs)[7]	x	x[8]	x	x	x[8]	x	x	x[8]	x	x	x[8]	x[8]	x[8]
Lipid panel	x	x[8]			x[8]			x[8]			x[8]	x[8]	x[8]
Urinalysis	x	x		x		x			x		x	x	x
Hemolysis profile[9]		x									x		
General immunology													
Rheumatoid factor	x	x									x	x	x

Table A-46 Schedule of Assessments, continued

	Week (± 3 days)												
	-3* SC	0* BL	2	4	6	8	12	14	16	20	24 WD 1	28 WD 2	32 WD 3
ANA (if pos.: anti-dsDNA)		x							x		x	x	x
Quantitative Ig		x									x	x	x
Complement (C3, C4)		x							x		x	x	x
PK/PD samples including tocilizumab, IL-6, sIL-6R, anti-tocilizumab antibodies and biomarkers[10]													
			All patients[11]										
Tocilizumab[12]		x[13]	x[14]	x[14]	x[14]	x[14]	x[13]	x[14]	x[14]	x[15]	x[13]		
IL-6[12]		x[13]	x[14]	x[14]	x[14]	x[14]	x[13]	x[14]	x[14]	x[15]	x[13]		
sIL-6R[12]		x[13]	x[14]	x[14]	x[14]	x[14]	x[13]	x[14]	x[14]	x[15]	x[13]		
Anti-tocilizumab antibodies (2 aliquots)[12]		x[13]	x[15]	x[15]	x[15]	x[15]	x[13]	x[15]	x[15]	x[15]	x[13]		
			Additional sample for subgroup of patients[16]										
Post-dose tocilizumab[17]		x		x			x						
			Biomarker sample for storage[18]										
Serum[12]		x	x	x					x		x		

WD = Withdrawal visit – assessments were performed at the time of premature withdrawal.
*The screening visit (SC) could occur up to 3 weeks prior to the first dose of double-blind study treatment and the baseline visit (BL) and randomization could occur up to 3 days prior to the first dose of double-blind study treatment.

1. Included in Medical History, and recorded in the CRF at baseline: the presence or absence of fibromyalgia and coronary heart disease risk factors
2. Pregnancy tests were conducted for female patients of child bearing potential
3. Vital signs were to be taken pre-dose and every 30 minutes during and 30 minutes after the infusion
4. Tocilizumab/placebo infusion could be administered up to 3 days after the study visit at which the protocol-designated study assessments were conducted
5. At the screening visit, two ECGs were taken at least 2 minutes apart
6. SAA, serum ferritin and haptoglobin were analyzed as safety parameters
7. If ALT, AST or bilirubin were > 2 times ULN, a coagulation profile was performed
8. Overnight fasting
9. To be performed at baseline and week 24 and if bilirubin was elevated during the study
10. All samples were taken from a single blood draw and aliquoted according to the aliquoting procedures in the laboratory manual
11. All samples were taken from a single blood draw. Samples were then either analyzed or stored depending on the visit and whether they had consented to participate as part of the 30% of the population undergoing population PK
12. Samples were to be taken pre-dose on dosing days
13. Sample was to be analyzed in all patients
14. Sample was to be analyzed in 30% of the population who had consented to additional PK, and stored for all other patients for potential analysis on a case-by-case basis
15. Sample was to be stored for all patients
16. Samples were to be taken in approximately 30% of the population who had consented to participate in the additional PK
17. Sample was to be taken within 15 minutes following completion of the infusion
18. Samples were to be taken only in patients who had consented to a sample being taken and stored for biomarker analysis

Note: on dosing days, blood samples for routine safety, immunology and storage were to be taken pre-dose.

Table 1 of WA17822 CSR

Table A-47, Schedule of Assessments for Patients on Escape Treatment in Study WA17822

	Week (± 3 days)						
	16	18	20	22	24 WD 1	28 WD 2	32 WD 3
Pregnancy test (urine)[2]	x		x		x		
Physical examination					x		
Vital signs, weight	x[2]		x[2]		x	x	x
Study drug infusion[3]	x		x				
Concomitant medications	x	x	x	x	x	x	x
ECG					x		
Efficacy							
Joint counts	x		x		x		
PT/INV global	x		x		x		
Pain VAS	x		x		x		
HAQ	x		x		x		
FACIT-fatigue	x		x		x		
SF-36			x		x		
Medical resource utilization	x		x		x		
EQ-5D			x		x		
WPAI			x		x		
High sensitivity CRP	x	x	x	x	x		
ESR	x	x	x	x	x		
SAA[4]	x	x	x	x	x		
Serum ferritin[4]	x	x	x	x	x		
Haptoglobin[4]	x	x	x	x	x		
Safety							
Adverse events	x	x	x	x	x	x	x
Hematology (CBC)	x	x	x	x	x	x	x
Blood chemistry (including LFTs)[5]	x	x[5]	x	x	x[6]	x[6]	x[6]
Lipid panel		x[6]			x[6]	x[6]	x[6]
Urinalysis			x		x	x	x
Hemolysis profile[7]					x		
General immunology							
Rheumatoid factor					x	x	x
ANA (if pos.: anti-dsDNA)			x		x	x	x
Quantitative Ig					x	x	x
Complement (C3, C4)			x		x	x	x

Table A-47, Schedule of Assessments for Patients on Escape Treatment, continued

	Week (± 3 days)						
	16	18	20	22	24 WD 1	28 WD 2	32 WD 3
PK/PD samples including tocilizumab, IL-6, sIL-6R, anti-tocilizumab antibodies and biomarkers							
	All patients						
Tocilizumab[8]	x[9]	x[9]	x[9]	x[10]	x[11]		
IL-6[8]	x[9]	x[9]	x[9]	x[10]	x[11]		
sIL-6R[8]	x[9]	x[9]	x[9]	x[10]	x[11]		
Anti-tocilizumab antibodies (2 aliquots)[8]	x[9]	x[10]	x[10]	x[10]	x[11]		
	Biomarker sample for storage[12]						
Serum[8]	x				x		

WD = Withdrawal visit – assessments were performed at the time of premature withdrawal.
Visits could be performed ± 3 days.

1. Pregnancy tests were conducted for female patients of child bearing potential
2. Vital signs were to be taken pre-dose and every 30 minutes during and 30 minutes after the infusion
3. Tocilizumab/placebo infusion could be administered up to 3 days after the study visit at which the protocol-designated study assessments were conducted
4. SAA, serum ferritin and haptoglobin were analyzed as safety parameters
5. If ALT, AST or bilirubin were > 2 times ULN, a coagulation profile was performed
6. Overnight fasting
7. To be performed at baseline and week 24 and if bilirubin was elevated during the study
8. Samples were to be taken pre-dose on dosing days
9. Sample was to be analyzed in 30% of the population who had consented to additional PK, and stored for all other patients for potential analysis on a case by case basis
10. Sample was to be stored for all patients
11. Sample was only to be analyzed in all patients
12. Samples were to be taken only in patients who had consented to a sample being taken and stored for biomarker analysis.

Note: on dosing days, blood samples for routine safety, immunology and storage were to be taken pre-dose.

Table 2 of WA17822 CSR

Withdrawal assessments

Patients who withdrew prematurely from the study returned for follow-up safety assessments 4, 8 and 12 weeks after the last infusion of study treatment. Patients who had completed the study, but who had not enrolled and had not received study treatment in the long-term extension study, also returned for a safety follow-up assessment 8 and 12 weeks after the last infusion of study treatment.

Patients withdrawn from the study due to elevated liver function tests had repeat tests performed 3 to 5 days after withdrawal and then every 2 weeks until concentrations were decreasing. Thereafter, the patients were followed on a monthly basis until concentrations were within the normal range. If the patient's liver function tests had not returned to normal within 6 months (or sooner, if deemed necessary by the investigator), the protocol advised that an ultrasound and liver biopsy be performed.

Patients withdrawn from the study due to an absolute neutrophil count < 500/mm^3, were followed closely for signs of infection, with treatment given as deemed appropriate by the investigator, and had a repeat WBC count (with differential) performed weekly until the absolute neutrophil count was above 1500/mm^3. If the absolute neutrophil count did not return to above 1500/mm^3 within 2 months (or sooner, if deemed necessary by the investigator), the protocol advised that a bone marrow biopsy be performed.
Adverse events and other laboratory abnormalities, particularly those considered to be drug related, were to be followed until resolution or stabilization.

Efficacy Parameters

Primary efficacy parameter:

The primary endpoint was the proportion of patients with an ACR20 response at week 24. To achieve an ACR20 response required at least a 20% improvement, compared with baseline, in both tender and swollen joint counts, as well as in 3 out of 5 additional ACR core set variables: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, HAQ-DI and CRP. CRP was used primarily for the calculation of the ACR response; if missing, ESR was substituted.

The ACR core set variables were measured as follows:

1. **Swollen/tender joint count (SJC/TJC)**: 66 joints were assessed for swelling and 68 joints were assessed for tenderness. Joints were assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis or fused joints were not taken into consideration for swelling or tenderness.
2. **Patient's global assessment of disease activity**: the patient's overall assessment of their current disease activity was assessed on a 100 mm horizontal VAS. The left-hand extreme of the line was described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme as "maximum disease activity" (maximum arthritis disease activity).
3. **Physician's global assessment of disease activity**: the physician's assessment of the patient's current disease activity was assessed on a 100 mm horizontal VAS. The left-hand extreme of the line was described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme as "maximum disease activity".
4. **Patient's assessment of pain**: the patient's assessment of their current level of pain was assessed on a 100 mm horizontal VAS. The left-hand extreme of the line was described as "no pain" and the right-hand extreme as "unbearable pain".
5. **Acute Phase Reactants**: high sensitivity CRP was analyzed centrally. ESR was measured locally.
6. **Health Assessment Questionnaire Disease Index**: The Stanford HAQ-DI is a patient completed questionnaire specific for RA. The questionnaire consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating,

walking, hygiene, reach, grip, and activities. The questionnaire was provided in validated translation into the local languages at the participating sites and was scored based on the instructions from the Stanford University Medical Center.

Secondary efficacy parameters:

1. Proportion of patients with ACR50 and ACR70 responses at 24 weeks
2. Longitudinal generalized estimating equations (GEE) analysis of ACR20, ACR50 and ACR70 responses
3. Time to onset of ACR20, ACR50 and ACR70 response
4. Mean changes from baseline in the individual ACR core set parameters at 24 weeks
5. Area under the curve (AUC) of the ACRn
   ACRn was defined as each patient's lowest percent improvement from baseline in 3 measures: TJC (68 joints), SJC (66 joints), and the improved score achieved in at least 3 of the 5 remaining ACR core set parameters.
6. Change from baseline in the Disease Activity Score (DAS) 28 at 24 weeks
   The DAS28 score is a measure of the patient's disease activity and is calculated as follows:
   $(0.56 \times 28TJC) + (0.28 \times 28SJC) + (0.7 \times \log eESR) + (0.014 \times GH)$,
   where 28TJC and 28SJC are the tender and swollen joint counts from 28 joints and GH (global health) is the patient's global assessment of disease activity and ESR is in mm/hour. A DAS28 score of <2.6 corresponds with a remission according to the American Rheumatism Association criteria.
   ESR was to be used primarily as the acute phase reactant; however, as CRP was analyzed centrally and, therefore, expected to be more reproducible than ESR, which was analyzed locally, the DAS28 score was also calculated using the following formula based on CRP rather than ESR:
   $(0.56 \times 28TJC) + (0.28 \times 28SJC) + (0.36 \times \log e(CRP + 1)) + (0.014 \times GH) + 0.96$,
   where 28TJC and 28SJC are the tender and swollen joint counts from 28 joints and GH is the patient's global assessment of disease activity and CRP is in mg/L.
7. AUC of the mean DAS28
8. Proportion of patients with DAS28 < 2.6 at 24 weeks
9. Categorical DAS28 responders (European League Against Rheumatism [EULAR] response) at 24 weeks
   The EULAR response categories of good, moderate and no response are defined as shown:

	Change from Baseline in DAS28 Score to Week X		
DAS28 at Week X	**< -1.2**	**< -0.6 to ≥ -1.2**	**≥ -0.6**
≤ 3.2	Good response	Moderate response	No response
>3.2 to ≤ 5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

A reduction in the DAS28 score from baseline (ie, a negative number) represents an improvement in the patient's condition.

10. Change from baseline in hemoglobin at 24 weeks
11. Mean change in rheumatoid factor (RF) (IU/mL) at 24 weeks in those patients who were RF positive (+)
12. Proportion of patients who withdrew due to lack of sufficient therapeutic response
13. Proportion of patients in each treatment group who received escape therapy.
14. Health Assessment Questionnaire disability index (HAQ-DI), SF-36, and FACIT-fatigue scale scores at 24 weeks (these secondary efficacy parameters are presented in a separate section for quality of life assessments).

The primary and secondary endpoints, their analytical approaches and how missing data were imputed for them (pre-specified in the statistical analysis plan) are described in Tables A-48 and A-49 below, excerpted from the statistical review by Dr. Joan Buenconsejo. These endpoints were common to all the studies. Additional endpoints pertaining studies WA17823 and WA17824 are presented in section 9.4.2 and 9.4.3, respectively.

Table A-48 Primary Endpoint for WA17822, WA17823, WA17824, WA18062 and WA18063

Endpoint(s)	Patient population	Analytical approach	Missing Data Imputation
Proportion of patients with an ACR20* response at Week 24	Intent-to-treat † (primary) Per protocol ‡ (secondary)	Primary: Cochran-Mantel-Haenszel chi-squared test** with adjustment for the stratification factor applied at randomization. Secondary: - logistic regression including the stratification factor(s) applied at randomization in the model. - Time to first ACR20 using Kaplan-Meier estimates - Generalized estimating equations to compare the longitudinal probability of an ACR 20 response between treatment groups. The primary model will include: site (or region), treatment group, visit and treatment group by visit interaction. For WA17824, an extended Mantel-Haenszel statistic adjusting for the stratification factor(s) applied at randomization will be applied for the difference in proportion of ACR20 responders to produce a 95% confidence interval. The null hypothesis will be rejected if the lower limit of the two-sided 95% confidence interval for the difference in the proportion of ACR20 responders on TCZ minus MTX is ≥ -0.12.	Primary: - Patients who withdrew prematurely from the study will be classed as non responders from the date they withdrew. - Patients who receive escape therapy will be classed as non responders for all time points beyond the time point at which they first receive escape therapy. - Patients that do not have the required data (i.e. tender and swollen joint counts, and at least three of the five ACR core set variables) at baseline and at that specific time pint will be classed as non responders at that time point. - Patients that have had intra-articular injections of steroid within the 8 weeks prior to their week 24 assessment will classed as non responders at Week 24 only. - The tender and swollen joint counts will use the total derived using the last observation carried forward method (LOCF). - C-reactive protein (CRP) will be used primarily for the calculation of the ACR response, if missing, erythrocyte sedimentation rate (ESR) will be substituted. - The physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, and HAQ-DI components will be based on the raw results. Secondary: - LOCF for each of the components - For escape patients, value at the escape visit or if missing the last pre-escape/post baseline value will be carried forward - For withdrawal patients, value at the withdrawal or if missing, last efficacy assessment prior to withdrawal will be carried forward.

Source: Sponsor's submission package
* 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).
† The ITT analysis population will consist of all patients that are randomized and who receive at least one administration of study medication.
‡ The PP population will consist of patients meeting certain inclusion and exclusion criteria that have been deemed to have the potential to affect patient outcome in terms of efficacy.
** Only for Studies WA17822, WA17823, WA18062, and WA18063.

Table A-49 Secondary Endpoints Common to WA17822, WA17823, WA17824, WA18062 and WA18063

Study	Endpoint(s)	Patient population	Analytical approach
WA17822 WA17823* WA17824 WA18062 WA18063	- Proportion of patients with an ACR50 and ACR70 responses at Week 24 - Mean changes from baseline in the individual parameters of ACR core set at 24 weeks. - AUC of the ACRn - Longitudinal (GEE) analysis of ACR20, ACR50 and ACR70 responses. - Change in disease activity score (DAS28) from baseline at 24 weeks. - Proportion of patients classified as categorical DAS28 responders (EULAR response) at 24 weeks. - AUC of the mean disease activity score - HAQ, SF-37 and FACIT fatigue scale scores at 24 weeks. - Proportion of patients who withdraw due to lack of sufficient therapeutic response. - Proportion of patients in each treatment group who receive escape therapy. - Mean change in RF (IU/mL) at 24 weeks in those patients with + RF. - Proportion of patients with DAS28 score < 2.6 at 24 weeks - Time to ACR20, ACR50, and ACR70 response. - Change in Hemoglobin from baseline at 24 weeks.	Intent-to-treat † (primary) Per protocol ‡ (secondary)	Categorical variable: Cochran-Mantel-Haenszel chi-squared test** with adjustment for the stratification factor applied at randomization. Secondary: - logistic regression including the stratification factor(s) applied at randomization in the model. Continuous variable: Analysis of covariance Time to Analysis: Kaplan-Meier estimates Longitudinal data: Generalized estimating equation analysis

Source: Sponsor's submission package
*WA17823: Endpoints at Week 24. Does not include Time to ACR20, ACR50, and ACR70 response, as well as Change in hemoglobin from baseline at 24 weeks.
† The ITT analysis population will consist of all patients that are randomized and who receive at least one administration of study medication.
‡ The PP population will consist of patients meeting certain inclusion and exclusion criteria that have been deemed to have the potential to affect patient outcome in terms of efficacy.

9.4.1.2 WA17822 Study Conduct

Study WA17822 was conducted from 2-16-05 to 11-13-06.

Protocol Amendments

Two protocol amendments were implemented during the conduct of the study. A list of major protocol changes are given below.

1. First Amendment – Protocol Version B, dated February 2005, introduced the following changes:

- Removed the collection of RNA from biological samples
- Removed the collection of urine samples and storage for biomarker analysis and clarified that the additional consent only applied to stored serum samples for biomarker analysis
- Added further details on the stability of the infusion bag at room temperature and clarified the vein that was to be used for the infusion
- Added that immunization with a live or attenuated vaccine was prohibited for the duration of study participation
- Provided additional guidance on dose modification and withdrawal due to decreases in absolute neutrophil count
- Required two, rather than one, 12-lead electrocardiograms (ECGs) at screening
- Removed requirement for a chest radiograph upon treatment completion

- Added clarification that laboratory results of the acute phase reactants would be available to the investigator, site staff and sponsor personnel at the baseline and screening visits only, in order to maintain the blind
- Included PT, PTT and INR assessments at baseline
- Added secondary efficacy variables
  - Time to onset of ACR20, ACR50 and ACR70 by treatment group
  - Proportion of patients with DAS score < 1.6 at 24 weeks (corrected to < 2.6 in protocol version C – see below)
  - Change from baseline in hemoglobin at week 24
- Added that treatment requirements for patients with coronary heart disease risk factors were adapted to the National Cholesterol Education Program (NCEP) III guideline
- Added an additional follow-up visit 12 weeks after the last infusion of study treatment for patients who had not enrolled into the long-term extension study.

2. Second Amendment – Protocol Version C, dated November 2005, introduced the following changes:

- Modified exclusion criterion 17 to exclude 'clinically significant abnormalities on chest radiograph as determined by the investigator' rather than specifying 'granulomatous disease on chest radiograph'
- Add further clarification on exclusion criterion 19 (history of malignancies)
- Removed serum collections for biomarker analysis at weeks 6, 8, 12, 14, 20 and 28
- Added that patients could be re-screened on one occasion
- Added collection of red blood cell (RBC) data, where necessary, and to express reticulocyte levels as an absolute count
- Added definition of when worsening of RA should be recorded as an adverse event
- Added clarification that the CRF served as the source document for assessments of questionnaires, VAS and joint counts.
- Corrected methods and criteria for DAS28 remission in the statistical analysis section.

Protocol Violations

The number of major protocol violations requiring study withdrawal was small: only a single patient in the placebo + MTX group and a single patient in the TCZ 4 mg/kg + MTX group. Of the deviations resulting in exclusion from the "Per-Protocol" analysis population, inclusion/exclusion criteria violations were the most common, ranging from 10% of patients enrolled into the placebo + MTX group to 14% of the patients enrolled into the TCZ 8 mg/kg + MTX group. The number of patients experiencing deviations that could possibly affect the Week 24 primary endpoint assessment was very low overall and deviations were distributed similarly among the treatment groups. Therefore these

protocol deviations are unlikely to have biased the results of the primary efficacy analysis or compromised the overall integrity of the study data.

Table A-50 WA17822 Protocol Deviations

Protocol Deviations for Study WA17822 (ITT Population)			
	Placebo + MTX n (%)	TCZ 4mg/kg + MTX n (%)	TCZ 8 mg/kg + MTX n (%)
Enrolled	204	213	205
Met requirements for Per Protocol Pop	168 (82)	164 (77)	169 (82)
Excluded from Per Protocol Pop	36 (18)	49 (23)	37 (18)
Protocol violation resulting in withdrawal	1	1	0
Reasons for exclusion pertaining to protocol violations (more than one may apply per patient)			
Inclusion/Exclusion criteria violations	20 (10)	26 (12)	28 (14)
Medication or randomization error	1	3	3
Change in corticosteroid within 4 weeks of Wk 24 assessment	4	3	6
Received change in NSAID dose within 2 wks of Wk 24	2	2	2
Received intra-articular steroids in violation of protocol specification	-	2	2
Received IM or IV corticosteroids	4	5	1
Joint counts not performed by independent assessor	2	1	2
Blinding compromised due to code breaks	4	1	-

Source: Tables 6 & 9 of WA17822 CSR

Patient disposition, baseline demographics, baseline disease characteristics have been discussed in conjunction with the 4 other pivotal studies in section 6.1.3 Demographics, and section 6.1.4 Patient Disposition, above. These conclusions apply to the individual study data for WA17822 reported here. To limit redundancy, results are presented in tabular format but will not be discussed in detail.

Table A-51 Patient Disposition for Study WA17822

Patient Disposition for Study WA17822 (ITT Population)			
	Placebo + MTX n (%)	TCZ 4mg/kg + MTX n (%)	TCZ 8 mg/kg + MTX n (%)
Enrolled	204	213	205
Completed	189 (93)	185 (87)	191 (93)
Entered Escape	68 (33)	31 (15)	19 (9)
Total discontinuations	15 (7)	28 (13)	14 (7)
Discontinuation due to AEs	8 (4)	16 (8)	12 (6)
SAEs (other than death)	1	5	4
Deaths	1	0	0
Other AE	6	11	8
Other withdrawals	7 (3)	12 (6)	2 (1)
Insufficient treatment effect	4	3	0
Protocol violation	1	1	0
Lost to follow-up	0	1	0
Patient choice	2	6	1
Other	0	1	1

Derived from Figure 2, Tables 6 and 7 and pg. 170-171 of WA17822 CSR

Table A-52 Baseline Demographics for Study WA17822

Baseline Demographics for Study WA17822 (ITT Population)			
	Placebo + MTX n = 204 n (%)	TCZ 4mg/kg + MTX n = 213 n (%)	TCZ 8 mg/kg + MTX n = 205 n (%)
Gender			
Female	159 (78)	175 (82)	175 (85)
Male	45 (22)	38 (18)	30 (15)
Age (years)			
mean	50.6	51.4	50.8
range	22-81	20-78	20-77
Height (cm)			
mean	163.1	161.6	161.6
range	140-199	136-191	133-181
Weight (kg)			
mean	71.6	69.9	68
range	41-125	37-148	40-123
Race			
White	149 (73)	159 (75)	148 (72)
Asian	25 (12)	22 (10)	25 (12)
Native American	19 (9)	22 (10)	19 (9)
Black	1 (<1)	1 (<1)	2 (<1)
Other	10 (5)	9 (4)	11 (5)
Ethnicity			
Hispanic	63 (31)	68 (32)	62 (30)
Non-Hispanic	138 (68)	144 (68)	143 (70)
Not known	1 (<1)	1 (<1)	n/a

Adapted from Table 10 of WA17822 CSR

Table A-53 Baseline Disease Characteristics for Study WA17822

Baseline Disease Characteristics for Study WA17822 (ITT Population)			
	Placebo + MTX n = 204 n (%)	TCZ 4mg/kg + MTX n = 213 n (%)	TCZ 8 mg/kg + MTX n = 205 n (%)
Duration of RA (years)			
mean	7.8	7.4	7.5
range	0.2 - 38.2	0.5 - 46.5	0.2 - 39.5
Number prev. DMARDs or TNF inhibitors			
mean	1.7	1.5	1.5
range	0-8	0-8	0-6
Baseline RF			
negative	60 (29)	46 (22)	34 (17)
positive	144 (71)	167 (78)	171 (83)
DAS 28			
mean	6.8	6.8	6.8
range	4.0 - 8.8	4.3 - 9.2	3.8 - 8.9
Oral steroid use			
no	93 (46)	96 (45)	93 (45)
yes	111 (54)	117 (55)	112 (55)
Baseline MTX dose (mg/wk)			
mean	14.8	14.7	14.5
range	10 - 25	8 - 25	10 - 25

Adapted from Table 11 of the WA17822 CSR

Table A-54 Baseline Disease Activity for Study WA17822

Baseline Disease Activity, ACR Core Response Variables for Study WA17822 (ITT Population)			
	Placebo + MTX n = 204	TCZ 4mg/kg + MTX n = 213	TCZ 8 mg/kg + MTX n = 205
Tender joint count			
mean	32.8	33.2	31.9
range	8 - 68	5 - 68	8 - 68
Swollen joint count			
mean	20.7	20.0	19.5
range	6 - 63	6 - 56	6 - 61
ESR (mm/hr)			
mean	49.7	49.2	51.2
range	2 - 130	1 - 140	2 - 139
CRP (mg/dL)			
mean	2.4	2.8	2.6
range	.07 - 16.3	.05 - 18.5	.02 - 18.6
HAQ-DI			
mean	1.5	1.6	1.6
range	0 - 3	0 - 3	0 - 3
Pain VAS (100 mm)			
mean	57.3	60.7	59.9
range	10 -100	12 - 100	2 - 100
Patient Global VAS (100 mm)			
mean	63.7	63.6	64.0
range	27 - 97	23 - 99	13 - 100
Physician Global VAS (100 mm)			
mean	63.7	63.6	64.0
range	27 - 97	23 - 99	13 - 100

Adapted from Table 13 of the WA17822 CSR

Efficacy Results

Refer to Section 6. Integrated Review of Efficacy, which contains the individual study results for WA17822 and each of the pivotal studies.

Safety Results

Refer to section 7 Integrated Review of Safety.

9.4.2 Study WA17823

9.4.2.1 WA17823 Study Protocol

Overall Study Design

Study WA17823 is a 2-year (1st year double-blind, 2nd year open-label) randomized, double-blind, placebo-controlled study in 1196 patients with moderately to severely active RA with previous inadequate clinical response to MTX at a dose of at least 10-25 mg per week. This study is being conducted at 137 centers in 15 countries; 58 sites are in the US, and the total US patient population is 332 (28% of the total study population).

Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks, given in addition to background treatment with MTX 10 to 25 mg (stable dose) weekly. Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue unchanged for the initial 24 weeks of the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy. Because the study is to remain blinded through Week 52, patients entering escape at week 16 were assigned doses in an automated fashion using the Interactive Voice Response System (IVRS). Those patients initially assigned to receive 4 mg/kg or 8 mg/kg TCZ were assigned to receive 8 mg/kg TCZ as escape treatment; patients initially assigned to placebo were assigned to receive 4 mg/kg TCZ as escape treatment. If after 3 doses or more of this escape therapy (which would occur after Week 24, and is therefore not germane to the interim data submitted in this BLA), patients who continued to show less than 20% improvement from baseline in both SJC and TJC would undergo another escape step whereby they would receive 8 mg/kg TCZ as open-label treatment.

The primary endpoint for the interim analysis submitted was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. For this interim analysis, only the study statistician was involved in the unblinding and analysis of the data post database lock,

and this person was removed from the conduct of the ongoing study. The study will be fully unblinded for the radiographic analysis at Week 52.

Figure A-18 WA17823 Study Schema

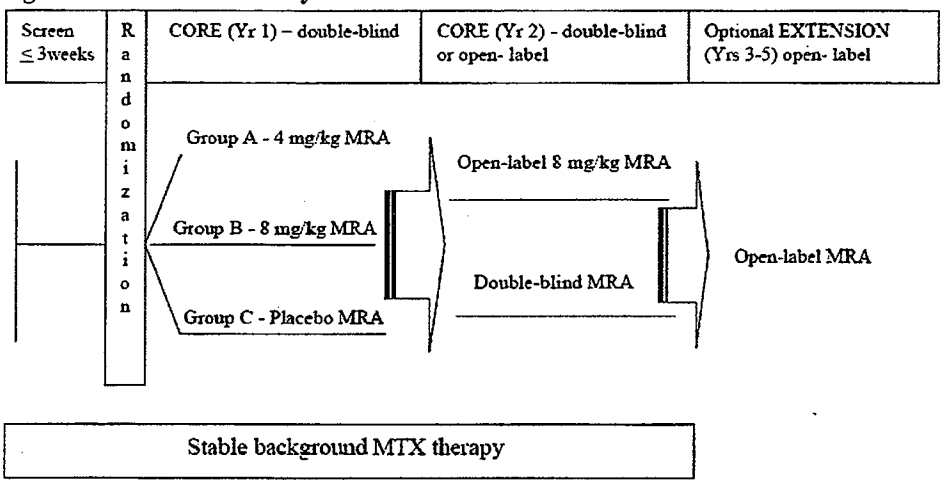


Figure 1 of WA17823 CSR

During year 1 of the core study, patients receive an infusion of tocilizumab or matching placebo in a blinded fashion, every 4 weeks, for a total of 13 infusions. Patients who failed to respond to treatment (i.e., achieved less than a 20% improvement in both the swollen joint count [SJC] and tender joint count [TJC]) after 16 weeks of blinded therapy were offered escape therapy with tocilizumab.

Patients who achieved less than a 20% improvement from baseline in both SJC and TJC, could, if requested and deemed necessary by the investigator, stop treatment to receive escape therapy and/or receive intra-articular steroids or an increase in oral corticosteroid dosage (up to a maximum dose of 10 mg per day). The option to receive escape therapy with tocilizumab was only for patients who had received two scheduled consecutive doses of double blind-medication prior to an escape decision being made. For instance, escape decisions could be considered at week 16 only for patients who received their scheduled double-blind medication at weeks 8 and 12. Patients who discontinued from the study prior to week 16 (for any reason) were not eligible to receive tocilizumab as escape therapy. Patients who received escape therapy were considered as non-responders in the efficacy analysis.

Tocilizumab escape therapy dosing occurred in a stepwise fashion (shown in Table A-55) and remained double-blind through step 1.

Table A-55 Escape Therapy

Randomized Treatment (for ≥ 16 weeks)	1st step Tocilizumab Escape (for ≥ 12 weeks duration)	2nd step Tocilizumab Escape (for ≥ 12 weeks duration)
Group A: 4 mg/kg tocilizumab	8 mg/kg tocilizumab	8 mg/kg tocilizumab
Group B: 8 mg/kg tocilizumab	8 mg/kg tocilizumab	8 mg/kg tocilizumab
Group C: Placebo	4 mg/kg tocilizumab	8 mg/kg tocilizumab

The tocilizumab escape dose was determined by the IVRS based on the initial treatment arm to which the patient was randomized. If after three doses or more of first step tocilizumab escape therapy, patients continued to show less than a 20% improvement from baseline in both SJC and TJC, they could receive the second step of tocilizumab escape therapy through week 52. If after three doses of the second step of tocilizumab escape therapy (8 mg/kg) a patient continued to show less than a 20% improvement from baseline in both SJC and TJC, treatment with tocilizumab was discontinued.

Inclusion Criteria

Inclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol) with the following addition:

1. Radiographic evidence of at least one joint with a definitive erosion attributable to RA as determined by the central reading site. Any joint of the hands, wrist or feet were considered with the exception of the distal interphalangeal joints of the hands.

Exclusion Criteria

Exclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

Concomitant Medications

In addition to tocilizumab or placebo, all patients received MTX at a stable pre-entry dose of between 10 and 25 mg/week. The dose and route of administration of MTX at entry into the study was to be continued without change while the patient was on double-blind therapy (i.e. for 52 weeks). Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs were permitted during the study provided the dose was stable for at least 6 weeks prior to baseline. All patients received at least 5 mg folate on a weekly basis.

Immunization with a live or attenuated vaccine was prohibited within 4 weeks prior to baseline and for the duration of study participation, including the 12 week follow-up period after administration of the last dose of infused study medication.

Methotrexate: Dose reductions for MTX or a change of route of administration were allowed at anytime for safety reasons.

NSAID (including COX-2 inhibitors) were allowed throughout the study, up to their maximum recommended dose. The choice and dose of NSAIDs was at the discretion of the investigator. Increases in the NSAID dose were not allowed over the first 52 weeks of the study and were to be avoided. Dose adjustments were permitted for safety reasons and, if absolutely required, to treat disease flares. Aspirin (maximum 350 mg/day) was allowed to reduce cardiovascular risk.

Oral corticosteroids: Increases in corticosteroids for treatment of RA were not allowed during the first 52 weeks of the study and were to be avoided. To treat non-RA conditions, such as asthma, increased doses of oral corticosteroids, up to 40 mg of prednisone daily (or equivalent) for 2 weeks or less was permitted. The corticosteroid dose was to be tapered down to the previous level as rapidly as medically possible.

Intravenous, intramuscular or intra-articular corticosteroids: Intravenous or intramuscular corticosteroids were not permitted during the study. Intra-articular corticosteroids were not permitted within 6 weeks prior to baseline. Injection of intra-articular steroids while on blinded study medication was discouraged, but was allowed to a limited extent. No more than 1 joint per 24-week period could be injected during the core period of the study (years 1 and 2). No single injection could exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid could not exceed 80 mg of triamcinolone (or equivalent) during any 52-week period.

Analgesics (other than NSAIDs): Analgesics up to their maximum recommended doses were allowed for pain management, as needed. However, analgesics were to be avoided within 24 hours prior to a visit where clinical efficacy assessments were performed and recorded.

Proton pump inhibitors and H_2 receptor blockers: The current standard of care for patients receiving corticosteroids and/or NSAIDs is that they should also receive prophylactic treatment with proton pump inhibitors at the recommended dose or H_2-receptor blockers at the maximum recommended dose. Patients enrolled in this study were assessed and prophylactic treatment added according to the investigator's discretion and local standards of care.

Folate: In order to minimize MTX toxicity, all patients received folate or equivalent at a dose of at least 5 mg/week given as a single dose weekly or divided into daily doses, the regimen being dependent on the investigator's decision.
The use of additional DMARDs or other biologic DMARDs was strictly prohibited during the core study period.

Assignment to treatment group

Eligible patients were randomly assigned to one of the three treatment arms (placebo + MTX, tocilizumab 4 mg/kg + MTX or tocilizumab 8 mg/kg + MTX) in a ratio of 1:1:1. Randomization was performed centrally using IVRS and was stratified by site using a randomization list provided by Roche. Each patient had a unique randomization number which was linked to the patient's identification number (CRF number). Medication numbers (vial numbers) were assigned by the IVRS at each dosing visit, depending on the patient's weight and allocated treatment arm, so that the correct dosage was provided. For patients on escape therapy, the IVRS assigned the appropriate medication numbers for each visit so the patient received the appropriate escape treatment. The IVRS was contacted prior to each infusion to obtain the appropriate medication numbers for the escape therapy.

Blinding

Same as for WA17822, except that data are blinded until the last patient has completed year 1, the study clinical database is locked and the unblinding procedure is performed.

In order to minimize the risk of unblinding of investigational staff, monitors, central services (central lab), and the Roche Study Management Team (SMT) during the rest of the double-blind section of the study, the week 24 data analyses were performed by a selected group of Roche team members only and were not communicated to investigational staff, monitors or central services.

Drug Administration

Same as for WA17822.

Criteria for Withdrawal from Treatment or Study and Replacement Policy

Patients were free to withdraw from participating in the study at any time for any reason. The investigator also had the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violations, cure, administrative reasons or other reasons.

Following implementation of amendment E of the study protocol, all patients enrolled in the study were questioned again on the history of lower gastrointestinal (GI) disease at the next scheduled study visit. Patients without a history of lower GI disease could continue in the study as planned. For those with such a history (eg, diverticulitis, diverticulosis requiring antibiotic treatment or chronic ulcerative lower GI disease such as Crohn's disease and ulcerative colitis), the investigator was required to perform an assessment to determine whether it was in the patient's best interest to continue in the study or whether study treatment should be withdrawn. When it was determined that the

patient could continue in the study, the patient had to provide informed consent again. Patients with a history of lower GI disease, who continue in the study are being closely monitored for occurrence of symptoms of lower GI bleeding or ulceration. Patients who prematurely stopped study treatment, for any reason, were not replaced.

Dose Modification

Same as for WA17822.

Infusion Reactions

Same as for WA17822.

Schedule of Assessments

Table A-56 Schedule of Assessments for WA17823 Core Study Period Year 1

Week	Screen -3 weeks	Study Med Start/ Baseline	2 ± 3d	4 ± 3d	6 ± 3d	8 ± 3d	12 ± 3d	14 ± 3d	16 ± 3d	20 ± 3d	24 ± 3d	28 ± 3d	32 ± 3d	36 ± 3d	40 ± 3d	44 ± 3d	48 ± 3d	52 ± 3d
Informed Consent	x																	
Demographics	x																	
Medical History	x	x[7]																
Inclusion/Exclusion	x	x																
Pregnancy Test (urine)[1]	x	x		x		x	x		x	x	x	x	x	x	x	x	x	x
Physical Exam	x										x							x
Vital Signs/Weight	x	x[2]		x[2]		x[2]	x[2]		x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	
Study Drug Infusion[3]		x		x		x	x		x	x	x	x	x	x	x	x	x	
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x[13]										x							x
CXR	x																	x

Table A-56 Schedule of Assessments for WA17823 Core Study Period Year 1 (cont.)

Week	Screen -3 weeks	Study Med Start/ Baseline	2 ± 3d	4 ± 3d	6 ± 3d	8 ± 3d	12 ± 3d	14 ± 3d	16 ± 3d	20 ± 3d	24 ± 3d	28 ± 3d	32 ± 3d	36 ± 3d	40 ± 3d	44 ± 3d	48 ± 3d	52 ± 3d
Efficacy																		
Joint counts	x	x	x	x		x	x		x	x	x	x	x	x	x	x	x	x
PT/INV Global		x	x	x		x	x		x	x	x	x	x	x	x	x	x	x
Morning Stiffness		x	x	x		x	x		x	x	x	x	x	x	x	x	x	x
Pain VAS		x	x	x		x	x		x	x	x	x	x	x	x	x	x	x
Radiographs[18]	x										x							x
HAQ		x	x	x		x	x		x	x	x	x	x	x	x	x	x	x
Fatigue (FACIT-F)		x	x	x		x	x		x	x	x	x	x	x	x	x	x	x
Health survey (SF-36)		x				x			x		x		x		x			x
Medical Resource Utilization		x		x		x	x		x	x	x	x	x	x	x	x	x	x
EQ-5D		x				x			x		x		x		x			x
WPAI		x				x			x		x		x		x			x
High Sensitivity CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ESR	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAA		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum ferritin		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Haptoglobin		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety																		
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Routine Labs																		
Hematology (CBC)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood Chemistry[12] (including LFTs)	x	x[4]	x	x	x[4]	x	x	x[4]	x	x	x[4]	x	x	x[4]	x	x	x	x[4]
Lipid Panel	x	x[4]			x[4]			x[4]			x[4]			x[4]				x[4]
Urinalysis	x	x		x		x			x		x		x		x			x
Hemolysis Profile[5]		x									x							x
Liver Function Profile		x																

Table A-56 Schedule of Assessments for WA17823 Core Study Period Year 1 (cont.)

Week	Screen -3 weeks	Study Med Start/ Baseline	2 ± 3d	4 ± 3d	6 ± 3d	8 ± 3d	12 ± 3d	14 ± 3d	16 ± 3d	20 ± 3d	24 ± 3d	28 ± 3d	32 ± 3d	36 ± 3d	40 ± 3d	44 ± 3d	48 ± 3d	52 ± 3d
General Immunology Labs																		
Rheumatoid factor	x	x									x							x
ANA (anti-dsDNA if ANA is positive)		x							x		x							x
Quantitative Ig		x									x							x
Complement (C3, C4)		x							x		x							x
PK/PD samples including: tocilizumab, IL-6, sIL-6R, anti-tocilizumab anti-bodies and biomarkers[6]																		
All Patients[8]																		
Tocilizumab[9]		x[14]	x[15]	x[14]	x[15]	x[15]	x[15]	x[15]	x[15]	x[16]	x[14]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[14]
IL-6[9]		x[14]	x[15]	x[14]	x[15]	x[15]	x[15]	x[15]	x[15]	x[16]	x[14]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[14]
sIL-6R[9]		x[14]	x[15]	x[14]	x[15]	x[15]	x[15]	x[15]	x[15]	x[16]	x[14]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[14]
Anti-tocilizumab antibodies (2 aliquots)[9]		x[14]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[14]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[14]
Additional Sample for Subgroup of Patients[10]																		
Post-dose (tocilizumab)[17]		x					x											

Week	Screen -3 weeks	Study Med Start/ Baseline	2 ± 3d	4 ± 3d	6 ± 3d	8 ± 3d	12 ± 3d	14 ± 3d	16 ± 3d	20 ± 3d	24 ± 3d	28 ± 3d	32 ± 3d	36 ± 3d	40 ± 3d	44 ± 3d	48 ± 3d	52 ± 3d
Biomarker Sample for Storage[11]																		
Serum[9]		x	x	x		x			x		x							x

1 Pregnancy tests conducted for female patients of child bearing potential
2 On infusion days vital signs were to be taken pre-dose, every 30 minutes during and 30 minutes after the infusion
3 Tocilizumab/placebo infusion could be administered up to 3 days after study visit at which the protocol-designated study-assessments were conducted
4 Overnight fasting (> 8 hours)
5 Performed at baseline, weeks 24, 52 and at the first follow-up visit (week 104), and when total bilirubin was elevated during the study
6 All samples were to be taken from a single blood draw and aliquoted according to the procedures in the laboratory manual
7 Included in medical history, and recorded in the CRF at baseline: the presence or absence of fibromyalgia and coronary heart disease risk factors
8 All samples were to be taken from a single blood draw. Samples were then either analyzed or stored depending on the visit and whether they had consented to participate as part of the 20% PK population
9 Sample was to be taken pre-dose on dosing days
10 Sample was to be taken for analysis in approximately 20% of patients at selected centers only who had consented to participate in the additional PK
11 Sample was only to be taken in consenting patients and stored for biomarker analysis
12 When ALT, AST or bilirubin were > 2x ULN, a liver function profile was to be performed
13 At the screening visit, 2 ECGs were to be taken at least 2 minutes apart
14 Samples that were to be analyzed in all patients
15 Samples that were to be analyzed in 20% of the population who had consented to additional PK, and stored for all other patients for potential safety analysis on a case by case basis
16 Sample were to be stored for all patients for potential safety analysis on a case by case basis
17 Sample was to be taken within 15 minutes of completing infusion
18 An additional radiograph was to be performed at the time of the patient's withdrawal or escape, when the last scheduled radiograph was taken more than 60 days prior to discontinuation of double blind study medication; however, when the radiograph performed at the time of withdrawal / escape was within the days prior to the scheduled assessment, the radiograph did not need to be repeated at the scheduled time point

Note: On dosing days, blood or urine samples for routine safety, immunology and storage were to be taken pre-dose.

Table 2 of WA17823 CSR

Withdrawal assessments

Patients who withdrew prematurely from the study returned for follow-up assessments 4, 8 and 12 weeks after the last infusion of study treatment. The follow-up visit 4 weeks after the last infusion included all assessments detailed for the week 24 visit, with the

exception of study medication infusion and addition of a chest X-ray. At the visits 8 and 12 weeks after the last infusion, vital signs were measured, concomitant medications and adverse events were recorded, and samples for routine laboratory and general immunology laboratory parameters were collected. Patients who had completed the study, but had not enrolled and had not received study treatment in the long-term extension study, also returned for a safety follow-up assessment 8 and 12 weeks after the last infusion of study treatment.

Patients withdrawn from the study due to elevated liver function tests (LFT) parameters had repeat tests performed 3 to 5 days after withdrawal and then every 2 weeks until concentrations began to decrease. Thereafter, patients were followed on a monthly basis until concentrations were within the normal range. If the patient's LFT parameters had not returned to normal within 6 months (or sooner, if deemed necessary by the investigator), the protocol advised that an ultrasound and liver biopsy be performed.

Patients withdrawn from the study due to an ANC < 500/μL were followed closely for signs of infection, with treatment given as deemed appropriate by the investigator. A repeat WBC count (with differentials) was also performed weekly until the ANC was above 1500/μL. If the ANC did not return to above 1500/μL within 2 months (or sooner, if deemed necessary by the investigator), the protocol advised that a bone marrow biopsy be performed.

Adverse events and other laboratory abnormalities, particularly those considered to be drug related, were to be followed until resolution or stabilization.

Efficacy Parameters

Efficacy parameters were the same as for WA17822 and are discussed above in section 9.4.1.1 WA17822 Study Protocol.

The primary and secondary endpoints, their analytical approaches and how missing data were imputed for them (pre-specified in the statistical analysis plan) are described in Tables A-48 and A-49 above, excerpted from the statistical review by Dr. Joan Buenconsejo. These endpoints were common to all the studies. Additional endpoints pertaining studies WA17823 are as follows:

Table A-57 Additional Primary Endpoints for WA17823

Endpoint(s)	Patient population	Analytical approach	Missing Data Imputation
Change from baseline in Modified Sharp total radiographic score at Week 52 (12 months) and at Week 104 (24 months)	Intent-to-treat † (primary) Per protocol ‡ (secondary)	No information	
Change in physical function as measured by the area under the curve for the change from baseline in the Health Assessment Questionnaire Disability Index at week 52 and at week 104.	Intent-to-treat † (primary) Per protocol ‡ (secondary)	No information	The primary method of analysis of the HAQ-DI score, no imputation of missing will be made, other than for missing baseline scores, for which last score prior to baseline with be carried forward.

Source: Sponsor's submission package
† The ITT analysis population will consist of all patients that are randomized and who receive at least one administration of study medication.
‡ The PP population will consist of patients meeting certain inclusion and exclusion criteria that have been deemed to have the potential to affect patient outcome in terms of efficacy.

Table A-58 Additional Secondary Endpoints after Week 24 for WA17823

Study	Endpoint(s)	Pt. population	Analytical approach
WA17823	Endpoints post Week 24: - Proportion of patients who achieve an improvement of at least 0.3 units from baseline in the HAQ disability index at 52 and 104 weeks. - Proportion of patients with ACR20, ACR50 and ACR70 responses at 52 and 104 weeks. - Proportion of patients with ACR70 response maintained for 6 consecutive months. - Mean changes from baseline in the individual parameters of ACR core set at 52 and 104 weeks. - AUC of the ACRn to 52 and 104 weeks - Longitudinal (GEE) analysis of ACR20, ACR50 and ACR70 responses to 52 and 104 weeks. - Change in disease activity score (DAS28) from baseline at 52 and 104 weeks. - Proportion of patients classified as categorical DAS28 responders (EULAR response) at 52 and 104 weeks. - Proportion of patients with DAS28 score < 2.6 at 52 and 104 weeks - AUC of the mean disease activity score at 52 and 104 weeks - Change from baseline in modified Sharp total radiographic score to weeks 24 and 80. - Change from baseline in erosion score to weeks 24, 52, 80, and 104. - Change from baseline in joint space narrowing score to weeks 24, 52, 80, and 104. - Proportion of patients with no progression of erosion by number of new erosions at 24, 52, and 104 weeks. - Proportion of patients with no progression of joint space narrowing by number of new joint space narrowing at 24, 52, and 104 weeks. - HAQ, SF-37 and FACIT fatigue scale scores at 52 and 104 weeks. - Mean change in RF (IU/mL) at 24 weeks in those patients with + RF. - Proportion of patients who withdraw due to lack of sufficient therapeutic response. - Proportion of patients in each treatment group who receive escape therapy. - Proportion of patients that achieved a remission according to the ACR remission criteria by Week 52 and 104. - Proportion of patients that achieved complete clinical response at Week 52 and 104.	Intent-to-treat † (primary) Per protocol ‡ (secondary)	Categorical variable: Cochran-Mantel-Haenszel chi-squared test[1x] with adjustment for the stratification factor applied at randomization. Secondary: - logistic regression including the stratification factor(s) applied at randomization in the model. Continuous variable: Analysis of covariance Time to Analysis: Kaplan-Meier estimates Longitudinal data: Generalized estimating equation analysis

9.4.1.2 WA17823 Study Conduct

Study Dates: December 14, 2004 to May 31, 2007.

Protocol Amendments

The protocol was amended four times during the conduct of this study.

1. First Amendment, Version B, October 24, 2004, prior to recruitment, introduced the following changes:

- Typographical errors and inconsistencies in the original synopsis and protocol were corrected, however, no major changes were implemented to the protocol in the first amendment.

2. Second Amendment, Version C, January 27, 2005, at which point less than 5% of patients had been recruited into the study, introduced the following changes:

- Removed the requirement for collection of urine samples for biomarker analysis and clarified that additional consent was required for collection and storage of biomarker samples for up to 15 years
- Added further details on the stability of the infusion bag at room temperature and clarified the vein that was to be used for the infusion
- Included granulomatous disease on chest X-ray as a criterion for exclusion (subsequently modified in amendment D)
- Simplified text regarding when dose reduction of NSAIDs and oral corticosteroids could be performed
- Added that immunization with a live or attenuated vaccine was prohibited for the duration of study participation
- Specified two (rather than one) ECG assessments at screening
- Added clarification that laboratory results of acute phase reactants would be available to the investigator, site staff and Roche personnel at the baseline and screening visits only, in order to maintain treatment-blind
- Included PT, PTT and INR assessments at baseline
- Clarified that blood samples for lipid assessments were to be collected in the fasted state
- Clarified that baseline (not screening) was the reference point for all analysis of radiographic endpoints
- Added the following secondary endpoints
    - time to onset of ACR20, ACR50 and ACR70 by treatment group
    - proportion of patients withdrawn due to lack of sufficient therapeutic response
    - proportion of patients in each treatment group who received escape therapy
- Allowed patients doing well on their double blind treatment in year 1 to remain on this blinded treatment in year 2 of the study
- Provided additional guidance on treatment discontinuation due to decreases in absolute neutrophil counts (ANC)
- Added a follow-up safety assessment 12 weeks (in addition to 4 and 8 weeks) after discontinuation of study drug to provide additional safety observation of patients

3. Third Amendment, Version D, November 4, 2005, at which point approximately 50% of patients had been recruited into the study, introduced the following changes:

- Added monitoring of morning stiffness to the schedule of assessments to allow for complete evaluation of clinical response and clinical remission
- Modified exclusion criterion 17 to exclude 'clinically significant abnormalities on chest radiograph as determined by the investigator' rather than specifying 'granulomatous disease on chest radiograph'
- Clarified exclusion criterion 19 on the history of malignancies
- Added that patients could be re-screened on one occasion only
- Removed the need to assess the hemolysis profile at weeks 108 and 112
- Added definition of when worsening of RA should be recorded as an adverse event
- Corrected methods and criteria for DAS28 remission in the statistical analysis section
- Added secondary study variables for assessment of clinical remission and complete clinical response
- Added clarification that the CRF served as the source document for certain assessments e.g., questionnaires, VAS and joint counts
- Changed time points for the collection of serum samples for biomarker analysis to bring them in line with the biomarker program in RA

4. Fourth Amendment, Version E, September 29, 2006, at which point over 80% of patients had been recruited into the study, introduced the following changes:

- Amended the study objectives and added an optional 3-year extension period at the end of the study in order to assess long-term safety and efficacy of tocilizumab administration
- Refined the blood sampling strategy to optimize the detection of anti-tocilizumab antibodies
- Added a more detailed description of the existing exclusion criteria concerning patients with a history of serious gastrointestinal disease (criteria 14 and 15), at the request of Health Authorities
- Provided details of the principal investigator for the study

Protocol Violations

The number of major protocol violations requiring study withdrawal was small: only two patients in the placebo + MTX group. Of the deviations resulting in exclusion from the "Per-Protocol" analysis population, inclusion/exclusion criteria violations were the most common, ranging from 9% of patients enrolled into the placebo + MTX group to 7% of the patients enrolled into the TCZ 8 mg/kg + MTX group. The number of patients experiencing deviations that could possibly affect the Week 24 primary endpoint assessment was very low overall and deviations were distributed similarly among the treatment groups. Therefore these protocol deviations are unlikely to have biased the

results of the primary efficacy analysis or compromised the overall integrity of the study data.

Table A-59 Protocol Deviations for Study WA17823

Protocol Deviations for Study WA17823 (ITT Population)			
	Placebo + MTX n (%)	TCZ 4mg/kg + MTX n (%)	TCZ 8 mg/kg + MTX n (%)
Enrolled	394	401	401
Met requirements for Per Protocol Pop	338 (86)	347 (87)	359 (90)
Excluded from Per Protocol Pop	54 (14)	52 (13)	40 (10)
Protocol violation resulting in withdrawal	2	-	-
Reasons for exclusion pertaining to protocol violations (more than one may apply per patient)			
Inclusion/Exclusion criteria violations	35 (9)	32 (8)	29 (7)
Medication or randomization error	2	4	1
Change in corticosteroid within 2 weeks of Wk 24 assessment	3	5	1
Received change in NSAID dose within 2 wks of Wk 24	1	2	1
Received intra-articular steroids in violation of protocol specification	6	3	3
Received IM or IV corticosteroids	5	7	2
Joint counts not performed by independent assessor	-	-	1
Blinding compromised due to code breaks	8	8	7

Source: Table 6 & 8 of WA17823 CSR

Patient disposition, baseline demographics, baseline disease characteristics have been discussed in conjunction with the 4 other pivotal studies in section 6.1.3 Demographics, and section 6.1.4 Patient Disposition, above. These conclusions apply to the individual study data for WA17823 reported here. To limit redundancy, results are presented in tabular format but will not be discussed in detail.

Table A-60 Patient Disposition for Study WA17823

Patient Disposition for Study WA17823 (ITT Population)			
	Placebo + MTX n (%)	TCZ 4mg/kg + MTX n (%)	TCZ 8 mg/kg + MTX n (%)
Enrolled	394	401	401
Withdrew before treatment	1	2	3
Randomized and treated	393*a	399*b	398*c
Completed	356 (91)	373 (93)	366 (92)
Entered Escape	150 (38)	67 (17)	41 (10)
Total discontinuations	36 (9)	26 (7)	33 (8)
Discontinuation due to AEs	12 (3)	16 (4)	22 (6)
SAEs (other than death)	4	7	3
Deaths	1	0	0
Other AE	7	9	19
Other withdrawals	24 (6)	10 (3)	11 (3)
Insufficient treatment effect	13	2	1
Protocol violation	2	0	0
Lost to follow-up	1	1	0
Patient choice	8	7	9
Other	1	0	1

* Used for ITT population calculations

a) number includes one patient who was randomized to placebo/MTX but received TCZ 4 mg/kg + MTX

b) number includes one patient randomized to placebo but received TCZ 4 mg/kg and excludes one patient who received TCZ 8 mg/kg

c) number excludes one patient randomized to TCZ 4 mg/kg but received TCZ 8 mg/kg

Derived from Figure 2, Tables 6, 7, 51 and p. 164-165 of the WA17823 CSR

Table A-61 Baseline Demographics for Study WA17823

Baseline Demographics for Study WA17823 (ITT Population)			
	Placebo + MTX n = 393 n (%)	TCZ 4mg/kg + MTX n = 399 n (%)	TCZ 8 mg/kg + MTX n = 398 n (%)
Gender			
Female	328 (83)	336 (84)	325 (82)
Male	65 (17)	63 (16)	73 (18)
Age (years)			
mean	51.3	51.4	53.4
range	19 - 82	21 - 84	18 - 84
Height (cm)			
mean	162.1	162.3	162
range	140 - 188	140 - 196	138 - 196
Weight (kg)			
mean	73.8	73.2	72.1
range	35 - 149	38 - 143	36 - 130
Race			
White	278 (71)	280 (70)	280 (70)
Asian	22 (6)	20 (5)	26 (7)
Native American	15 (4)	19 (5)	13 (3)
Black	16 (4)	23 (6)	21 (5)
Other	62 (16)	57 (14)	58 (15)
Ethnicity			
Hispanic	142 (36)	137 (34)	138 (35)
Non-Hispanic	251 (64)	262 (66)	260 (65)

Adapted from Table 9 of the WA17823 CSR

Table A-62 Baseline Disease Characteristics for Study WA17823

Baseline Disease Characteristics for Study WA17823 (ITT Population)			
	Placebo + MTX n = 393 n (%)	TCZ 4mg/kg + MTX n = 399 n (%)	TCZ 8 mg/kg + MTX n = 398 n (%)
Duration of RA (years)			
mean	8.9	9.4	9.3
range	0.5 - 44.3	0.5 - 43.2	0.6 - 49.9
Number prev. DMARDs or TNF inhibitors			
mean	1.6	1.7	1.6
range	0 - 10	0 - 8	0 - 6
Baseline RF			
negative	72 (18)	77 (19)	68 (17)
positive	321 (82)	322 (81)	330 (83)
DAS 28			
mean	6.5	6.5	6.6
range	3.7 - 9.0	3.6 - 8.8	3.7 - 8.9
Oral steroid use			
no	128 (33)	134 (34)	156 (39)
yes	265 (67)	265 (66)	242 (61)
Baseline MTX dose (mg/wk)			
mean	14.9	14.9	15.4
range	8 - 25	10 - 25	10 - 210*

* as listed in Table 10 of WA17823 CSR.

Table A-63 Baseline Disease Activity for Study WA17823

Baseline Disease Activity, ACR Core Response Variables for Study WA17823 (ITT Population)			
	Placebo + MTX n = 393	TCZ 4mg/kg + MTX n = 399	TCZ 8 mg/kg + MTX n = 398
Tender joint count			
mean	27.9	27.9	29.3
range	8 - 68	8 - 68	8 - 68
Swollen joint count			
mean	16.6	17.0	17.3
range	6 -65	6 - 66	6 - 66
ESR (mm/hr)			
mean	46.5	45.9	46.4
range	4 - 126	1 - 125	1 - 140
CRP (mg/dL)			
mean	2.2	2.1	2.3
range	.02 - 18.6	.02 - 16.8	.04 - 19.5
HAQ-DI			
mean	1.5	1.5	1.5
range	0 - 3	0 - 3	0 - 3
Pain VAS (100 mm)			
mean	55.3	53.3	55.7
range	0 - 100	0 - 100	0 - 100
Patient Global VAS (100 mm)			
mean	63.1	61.0	62.7
range	0 - 100	0 - 100	0 - 100
Physician Global VAS (100 mm)			
mean	63.1	62.3	62.7
range	14 - 100	3 - 99	3 - 100

Adapted from Table 12 of the WA17823 CSR

Efficacy Results

Refer to Section 6. Integrated Review of Efficacy, which contains the individual study results for WA17823 and each of the pivotal studies.

Safety Results

Refer to section 7 Integrated Review of Safety.

9.4.3 Study WA17824

9.4.3.1 WA17824 Study Protocol

Overall Study Design

Study WA17824 is a 24-week randomized, double-blind, parallel group non-inferiority study in 673 patients with moderately to severely active RA who had not been treated with MTX within 6 months prior to randomization, and who had not discontinued previous MTX treatment due to toxicity or lack of response. This study was conducted at 120 centers in 18 countries; 54 sites were in the US and the total US patient population was 211 (31% of the total).

Patients were randomized 1:1 to receive either TCZ 8 mg/kg IV every 4 week plus placebo MTX capsules or MTX oral capsules weekly plus placebo IV infusion every 4 weeks. MTX was provided in an escalating dose regimen starting at 7.5 mg weekly, increasing to 15 mg weekly at Week 4, then to 20 mg weekly at Week 8. Stable NSAID and corticosteroid (≤10 mg/day prednisone equivalent) were continued throughout the study. As an internal control for efficacy, some patients at centers in Canada, Israel, and the US were enrolled into a placebo-controlled substudy whereby they would receive 8 weeks total of placebo capsules and placebo IV infusions. At Week 8, patients received TCZ 8 mg/kg plus placebo MTX capsules for the remaining 16 weeks of the study. Only patients in this placebo-controlled substudy were eligible for escape treatment (to open-label TCZ 8 mg/kg) if they experienced a 20% increase in the number of active swollen and tender joints at any of the first 7 weekly visits.

The primary efficacy analysis, performed on the per-protocol population, was a non-inferiority comparison (pre-specified non-inferiority margin of 12%) of the proportion of ACR20 responders at Week 24 in the MTX group versus the TCZ 8 mg/kg group. If TCZ was shown to be non-inferior to MTX in ACR20 response at Week 24, testing for superiority was pre-specified.

After the completion of 24 weeks of randomized treatment, patients could either enter a "Transition Phase" or roll over to an open-label, long-term extension study (WA18696)

in which they would receive TCZ 8 mg/kg every 4 weeks for up to 5 years. Patients who achieved a ≥50% decrease in the number of active swollen and tender joints (compared to baseline) while receiving their current blinded study treatment at both Week 20 and Week 24 had the option of continuing their current blinded study treatment until the last patient enrolled into the study and the study database had been locked. Patients not maintaining this level of improvement could immediately enroll in WA18696 and receive open-label TCZ treatment. Approximately 101 patients entered the transition phase.

Figure A-19 WA17824 Study Schema

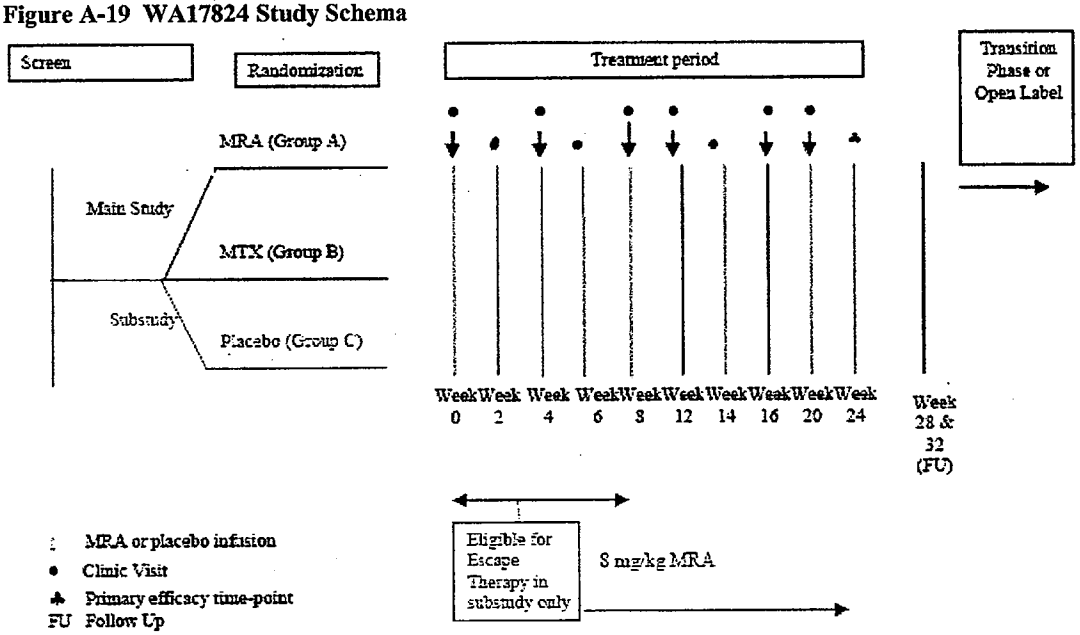


Figure 1 of WA17824 CSR

Inclusion Criteria

Inclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol) with the exception that RA duration could be ≥3 months, rather than ≥6 months.

Exclusion Criteria

Exclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol) with the following additions:

1. Treatment with MTX within 6 months prior to randomization.
2. Discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response as determined by the investigator.

Concomitant Medications

Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs were permitted during the study provided the dose was stable for at least 6 weeks prior to baseline.

Immunization with a live or attenuated vaccine was prohibited within 4 weeks prior to baseline and for the duration of study participation, including the 12 week follow-up period after administration of the last dose of infused study medication.

NSAIDs (including COX-2 inhibitors) were allowed throughout the study, up to their maximum recommended dose. The choice and dose of NSAIDs was at the discretion of the investigator. Alterations in NSAID dose were strongly discouraged for the first 24 weeks of the study. Dose adjustments were permitted for safety reasons and, if absolutely required, to treat disease flares. Aspirin (maximum 350 mg/day) was allowed to reduce cardiovascular risk.

Oral corticosteroids: Alterations in background oral corticosteroid dose were strongly discouraged for the first 24 weeks of the study. To treat non-RA conditions, such as asthma, increased doses of oral corticosteroids, up to 40 mg of prednisone daily (or equivalent) for 2 weeks or less was permitted. The corticosteroid dose was to be tapered down to the previous level as rapidly as medically possible.

Intravenous, intramuscular or intra-articular corticosteroids: Intravenous or intramuscular corticosteroids were not permitted during the study. Intra-articular corticosteroids were not permitted within 6 weeks prior to baseline. Injection of intra-articular steroids while on blinded study medication was discouraged, but was allowed to a limited extent. No more than one joint could be injected and no single injection could exceed 40 mg of triamcinolone (or equivalent). Injection of any joint within the first 8 weeks of the study and from Week 16 onwards resulted in the patient being excluded from the efficacy analysis at Week 8 and 24, respectively.

Analgesics (other than NSAIDs): Analgesics up to their maximum recommended doses were allowed for pain management, as needed. However, analgesics were to be avoided within 24 hours prior to a visit where clinical efficacy assessments were performed and recorded.

All DMARDs and non-biologic DMARDs other than the study treatments were prohibited.

Assignment to treatment group

In the main study approximately 350 patients were randomly assigned to two groups in a 1:1 ratio (placebo + MTX or tocilizumab 8 mg/kg + placebo). In the placebo controlled

substudy, approximately 300 patients were randomly assigned to three groups in a 1:1:1 ratio (placebo + MTX, tocilizumab 8 mg/kg + placebo or placebo for 8 weeks followed by tocilizumab 8 mg/kg + placebo for the remaining 16 weeks of the study).

Randomization was administered centrally via an interactive voice response system (IVRS) and was stratified by 'site' and disease duration (≤ 2 years / > 2 years) using a randomization list provided by Roche. A patient's eligibility was evaluated by the investigator to ensure that the inclusion and exclusion criteria were met and that the patient was eligible for participation in the study. Eligible patients were then randomized and assigned a unique randomization number. Medication numbers for the study (infusions and oral capsules) were assigned by the IVRS prior to dosing at each dosing visit depending on the patient's weight and allocated treatment arm in order to ensure that the correct dosage was provided.

Blinding

This was a blinded study, with the sponsor, investigators, and patients unaware of the treatment assignment of each patient. Study medication was administered as double dummy in order to maintain the blind. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment.

In order to maintain the double-blind status of the study, once infused study treatment had commenced, acute phase reactant data from the central laboratory were blinded to site and sponsor personnel. Results of the PK assays were also not available to the investigators and were blinded to the sponsor and monitors during the course of the study.

Drug Administration

1. Tocilizumab: Tocilizumab or placebo was administered intravenously every 4 weeks at Weeks 0 (Day 1), 4, 8, 12, 16 and 20 on an outpatient basis. Infusions were to be administered under close supervision of the investigator or sub-investigator, in a setting where resuscitation facilities were available. Two to six vials of tocilizumab or placebo were assigned to each patient for each infusion depending on the patient's bodyweight. As per the study exclusion criteria, the maximum weight dosed was 150 kg (ie, maximum 1200 mg dose). Tocilizumab/placebo was administered by controlled infusion into an arm vein over a one hour period. The infusion speed of the 100 mL infusion bag was to be 10 mL/hour for 15 minutes and then increased to 130 mL/hour to complete the dosing over 1 hour. Normal saline (20 mL) was administered following the infusion of study medication to flush the remaining study medication through the intravenous set.
In exceptional circumstances, it was allowable for the infusion time to be extended for up to 6 hours.

2. MTX: MTX or placebo was administered orally once a week starting at Week 0 (Day 1) and continuing up to and including Week 24. Patients started on 7.5 mg MTX weekly. At Week 4, if the patient had any swollen or tender joints, the MTX dose was increased to 15 mg. At Week 8, if the patient had any swollen or tender joints, the MTX dose was increased to 20 mg. For those patients taking ≥ 15 mg weekly, MTX was taken as two divided doses 12 hours apart. MTX was provided in 2.5 mg capsule strengths. One 5 mg reduction (2 capsules) in the dose of MTX or its placebo was allowed for patients who, in the opinion of the treating physician, experience dose limiting MTX related side effects. The dose was not be increased at any time after the dose had been reduced nor was the dose to be reduced to less than 4 capsules/week (10 mg/week). MTX / placebo capsules were to be taken weekly on the same day as the infusion, when they coincided. Patients on six or more capsules were to take them as two divided doses, 12 hours apart. Capsules were to be swallowed whole with 200 mL of still water. A record of the dates of intake of MTX was kept by the patient as an aide memoire and was reviewed by the treating physician at each visit.

3. Placebo: Patients assigned to Group C of the placebo controlled substudy received an i.v. infusion of placebo at Weeks 0 and 4, switching to tocilizumab 8 mg/kg at Week 8. Placebo MTX capsules, which were visually identical to the study-supplied MTX capsules (to maintain the blind), were administered as in Groups A and B.

4. Folic acid: As part of the inclusion criteria of this study, patients enrolled under version B and version C of the protocol were required to receive at least 5 mg folic acid weekly. This was to be administered either as daily doses or as single weekly doses following administration of MTX. Some patients who were enrolled under the first version of the protocol did not receive concomitant folic acid due to differences in local standard of care.

Criteria for Withdrawal from Treatment or Study and Replacement Policy

Patients were free to withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violations, cure, administrative reasons or other reasons.

All patients who withdrew from the study were to return for a Safety Follow-up assessment 4, 8 and 12 weeks after the last infusion. Adverse events and laboratory abnormalities, particularly those considered to be drug-related, were followed until resolution or stabilization.

All patients in the study were questioned about their medical history of lower GI disease. Patients without a history of lower GI disease could continue in the study as planned. In patients with such history (eg., diverticulitis, diverticulosis requiring antibiotic treatment

or chronic ulcerative lower GI disease such as Crohn's disease and ulcerative colitis) the investigator performed an assessment to determine if it was in the best interest of the patient to continue in the study or be withdrawn from the study treatment. If the investigator determined that the patient should continue in the study, the patient was required to give informed consent again. Patients with a history of lower GI disease, who continued in the study, were closely monitored for occurrence of symptoms of lower GI bleeding or ulceration. Prior to each study drug infusion the patient was questioned about GI-related signs and symptoms. In the event of new information in the patient's clinical history a focused GI evaluation was performed. Any clinically significant findings were documented as adverse events and study drug infusion was held pending further evaluation by the investigator based on his/her judgment. After reassessing the patient's status the investigator determined whether to continue study treatment or withdraw therapy.

Dose Modification

The following dose modification rules applied to patients receiving double blind study medication or escape therapy. To remain blinded, the following changes were made to oral and i.v. administration in response to liver function test elevations:

Oral Study Medication

1. ALT or AST Elevations:
   - In the event that a patient's ALT or AST was elevated to ≥ 5x ULN, treatment with the oral study medication was stopped permanently.
   - Patients who experienced a minor increase in ALT or AST less than 2x ULN continued treatment with study medication. Blood samples for repeat testing were taken every two to four weeks thereafter.
   - If a patient taking 3 capsules of study medication/week experienced an increase in ALT or AST ≥ 2x ULN but < 5x ULN, the oral study medication was suspended until the levels decreased to less than 2x ULN. If the patient missed more than seven consecutive doses oral study medication was permanently discontinued, however infusion of study medication continued.
   - If a patient taking 6-8 capsules of study medication/week experienced an increase in ALT or AST ≥ 2x ULN but < 5x ULN, the oral study medication was suspended for one week and up to two weeks if necessary. The oral study medication was then restarted at a dose reduced by 2 capsules.
   - If a patient, who had one dose reduction in oral study medication, experienced an increase in ALT or AST ≥ 2x ULN but < 5x ULN, the oral study medication was suspended until the levels decreased to < 2x ULN. If the patient missed more than 7 consecutive doses during this time oral study medication was permanently discontinued, however infusion of study medication continued.

Intravenous Study Medication

1. ALT or AST Elevations:

- In the event that a patient's ALT or AST was elevated to ≥ 5x ULN, treatment with the i.v. study medication was stopped permanently.
- Patients who experienced a minor increase in ALT or AST < 2x ULN continued infusion of study medication. Blood samples for repeat testing were taken every two to four weeks thereafter.
- If a patient had an ALT or AST elevation ≥ 2x ULN but < 3x ULN, the patient could receive the infusion of study medication (a blood sample was to be taken just prior to the infusion of study medication to verify that the ALT and AST remained below 3x ULN).
- If a patient had experienced an increase in ALT or AST ≥ 3x ULN, the i.v. study medication was suspended. Once the patient's ALT and AST were below 3x ULN, study treatment recommenced at the next scheduled 4 weekly visit.
- If the patient had a second ALT or AST elevation ≥ 3x ULN on recommencing treatment with the i.v. study medication, treatment was permanently discontinued.
- If two consecutive doses of i.v. study medication were missed due to ALT or AST elevations, treatment was permanently discontinued.

2. Bilirubin
   - If a patient experienced a level of indirect bilirubin ≥ 2x ULN or a total bilirubin value of > 43 μmol/L (2.5 mg/dL), treatment with oral and i.v. study medication was permanently discontinued.

3. Creatinine
   - If creatinine increased to ≥ 194 μmol/L (2.2 mg/dL) in women or ≥ 221 μmol/L (2.5 mg/dL) in men, study medications were held until the creatinine level had returned to baseline levels.
   - If two consecutive doses of i.v. study medication or seven consecutive doses of oral study medication were missed due to creatinine elevations, treatment with the study medication was discontinued permanently.

4. Infections
   - Clinical signs which should warn the investigator of possible drug toxicity include severe infection or frequent minor infections, mucositis and pneumonitis. The investigator was required to report such signs to the sponsor, provide appropriate treatment and reduce the dose of oral study medication (reduced by 2 capsules) or stop the study drugs if deemed necessary.

5. Neutrophils
   - If a patient's absolute neutrophil count (ANC) decreased to < 0.5 x 10^9/L (0.5 GI/L or 500/mm^3) during the study, treatment with study drug was discontinued permanently.

One 5 mg reduction (2 capsules) in the dose of MTX or its placebo was allowed for patients who, in the opinion of the treating physician, experienced dose limiting MTX related side effects. The dose was not to be increased at any time after the dose had been reduced nor was the dose to be reduced to less than 4 capsules/week (10 mg/week).

For study visits at which the study medication dose was held due to toxicity as described above, all other study assessments were performed as per study schedule.

The abnormal laboratory test values and infections referred to in this section were reported as Adverse Events.

Infusion Reactions

Same as for WA17822.

Schedule of Assessments

Table A-64 Schedule of Assessments for Study WA17824

Week	- 3 (SC)	0 (BL)	2 ±3d	4 ±3d	6 ±3d	8 ±3d	12 ±3d	14 ±3d	16 ±3d	20 ±3d	24 ±3d WD1	28 ±3d WD2	32 ±3d WD3
Informed Consent	x												
Demographics	x												
Medical History	x	x[1]											
Inclusion/Exclusion	x	x											
Pregnancy Test (urine)[2]	x	x		x		x	x		x	x	x		
Physical Exam	x										x		
Vital Signs, weight	x	x[3]		x[3]		x[3]	x[3]		x[3]	x[3]	x	x	x
Study drug infusion[4]		x		x		x	x		x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x[16]										x		
CXR	x												
Efficacy													
Joint counts	x	x	x	x		x	x		x	x	x		
PT/INV Global		x	x	x		x	x		x	x	x		
Pain VAS	x[15]	x[15]	x[15]	x[15]	x[15]	x	x		x	x	x		
Morning Stiffness		x	x	x		x	x		x	x	x		
HAQ-DI		x	x	x		x	x		x	x	x		
Fatigue (FACIT-F)		x		x		x	x		x	x	x		
SF-36		x				x			x		x		
Medical Resource Utilization		x		x		x	x		x	x	x		

Table A-64 Schedule of Assessments for Study WA17824 (continued)

Week	-3 (SC)	0 (BL)	2 ±3d	4 ±3d	6 ±3d	8 ±3d	12 ±3d	14 ±3d	16 ±3d	20 ±3d	24 ±3d WD1	28 ±3d WD2	32 ±3d WD3
High sensitivity CRP	x	x	x	x	x	x	x	x	x	x	x		
ESR	x	x	x	x	x	x	x	x	x	x	x		
SAA	x	x	x	x	x	x	x	x	x	x	x		
Serum ferritin	x	x	x	x	x	x	x	x	x	x	x		
Haptoglobin	x	x	x	x	x	x	x	x	x	x	x		
Safety													
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x
Routine Labs													
Hematology (CBC)	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood Chemistry (including LFTs)[5]	x	x[6]	x	x	x[6]	x	x	x[6]	x	x	x[6]	x[6]	x[6]
Lipid Panel	x	x[6]			x[6]			x[6]			x[6]	x[6]	x[6]
Urinalysis	x	x		x		x			x		x	x	x
Hemolysis profile[7]		x									x		
Liver Function Profile[5]		x											
Immunology Labs													
Rheumatoid Factor	x	x									x	x	x
ANA (if pos.: anti-dsDNA)		x							x		x	x	x
Quantitative Ig		x									x	x	x
Complement (C3, C4)		x							x		x	x	x

Table A-64 Schedule of Assessments for Study WA17824 (continued)

PK/PD samples including: MRA, IL-6, sIL-6R, anti-MRA antibodies [8]													
All Patients[9]													
MRA[10]		x[11]	x[12]	x[12]	x[12]	x[12]	x[11]	x[12]	x[12]	x[13]	x[11]		
IL-6[10]		x[11]	x[12]	x[12]	x[12]	x[12]	x[11]	x[12]	x[12]	x[13]	x[11]		
sIL-6R[10]		x[11]	x[12]	x[12]	x[12]	x[12]	x[11]	x[12]	x[12]	x[13]	x[11]		
Anti-MRA antibodies		x[11]	x[13]	x[11]	x[13]	x[11]	x[11]	x[13]	x[13]	x[13]	x[11]		
Additional Sample for Subgroup of Patients[14]													
Post-dose MRA (within 15 minutes		x		x			x						
Biomarker Sample for Storage[17]													
Serum[10]		x				x			x		x		
Blood (PAXgene tube for mRNA)[10]		X				x			x		x		

WD = Withdrawal visit – assessments performed at the time of premature withdrawal from the study.
WD1 assessments performed 4 weeks after last infusion; WD2 assessments performed 8 weeks after last infusion; WD3 assessments performed 12 weeks after last infusion.

1 Included in medical history and recorded in the CRF at baseline: the presence or absence of fibromyalgia and coronary heart disease risk factors
2 If of childbearing potential
3 Vital signs were taken pre-dose and every 30 minutes during and 30 minutes after the infusion
4 In addition, MTX or placebo capsules were given weekly up to and including week 24 as per the requirements of the protocol.
5 If ALT, AST or bilirubin were > 2 times ULN, a liver function profile was performed.
6 Overnight (>8 hours) fasting
7 At baseline and Week 24. In addition, reticulocytes, LDH (with isoenzymes), haptoglobin, bilirubin (total, direct and indirect) and Coombs test were to be tested if bilirubin was elevated during the study.
8 All aliquots were taken from a single blood draw regardless of whether they were analyzed or stored (apart from the post-dose sample).
9 All samples were taken in all patients. Samples were then either analyzed or stored depending on the visit and whether the patient had consented to participate in the additional PK sampling (10% of the population).
10 Sample was taken pre-dose on dosing days.
11 Sample analyzed in all patients.
12 Sample analyzed in 10% of the population who had consented to additional PK sampling, and stored for all other patients for potential safety analysis on a case by case basis.
13 Sample stored for all patients.
14 Approximately 10% of patients at selected centers who had consented to participate in additional PK sampling.
15 Pain VAS was taken daily for at least 7 days prior to baseline visit and then daily up to week 6
16 At screening, 2 ECGs were taken at least 2 minutes apart.
17 Sample was only taken in patients who had consented to a sample being taken and stored for biomarker analysis.

Note: i.v. study drug administration could occur within 3 days of the study assessments being performed.

Table 2 of WA17824 CSR

Withdrawal assessments

Patients who withdrew prematurely from the study returned for follow up safety assessments 4, 8 and 12 weeks after the last infusion of study treatment. Patients who had completed the study, but had not enrolled and had not received study treatment in the long-term extension study, also returned for a safety follow-up assessment 8 and 12 weeks after the last infusion of study treatment.

Patients withdrawn from the study due to elevated liver function tests had repeat tests performed 3 to 5 days after withdrawal and then every 2 weeks until concentrations began to decrease. Thereafter, patients were followed on a monthly basis until concentrations were within normal range.

Patients withdrawn from the study due to an absolute neutrophil count < 500/mm^3 were followed closely for signs of infection, with treatment given as deemed appropriate by the investigator. A repeat WBC count (with differential) was also performed weekly until the absolute neutrophil count was above 1500/mm^3.

Adverse events and other laboratory abnormalities, particularly those considered to be drug related, were to be followed until resolution or stabilization.

Efficacy Parameters

Efficacy parameters were the same as for WA17822 and are discussed above in section 9.4.1.1 WA17822 Study Protocol.

The primary and secondary endpoints, their analytical approaches and how missing data were imputed for them (pre-specified in the statistical analysis plan) are described in Tables A-48 and A-49 above, excerpted from the statistical review by Dr. Joan Buenconsejo. These endpoints were common to all the studies. Additional secondary endpoints pertaining to Study WA17824 are as follows:

Table A-65 Additional Secondary Endpoints for Study WA17824

Study	Endpoint(s)	Patient population	Analytical approach
WA17824	Additional: - The proportion of patients with an ACR20 response at Week 8. - Median time to improvement in daily pain VAS (25% decline in pain VAS from baseline). - Proportion of patients that achieved a remission according to the ACR remission criteria by Week 24.	Intent-to-treat † (primary) Per protocol ‡ (secondary)	

Source: Sponsor's submission package
† The ITT analysis population will consist of all patients that are randomized and who receive at least one administration of study medication.
‡ The PP population will consist of patients meeting certain inclusion and exclusion criteria that have been deemed to have the potential to affect patient outcome in terms of efficacy.

9.4.3.2 WA17824 Study Conduct

Study Dates: 7-6-05 to 4-23-07.

Protocol Amendments

The original protocol, dated March 14, 2005, was amended twice during the conduct of this study. A list of major protocol changes are given below.

1. First Amendment – Protocol Version B, was dated November 9, 2005 was made after patient enrollment began. Major protocol changes included the following:

- Clarifications were made regarding eligibility criteria for receiving escape therapy.
- Monitoring of morning stiffness was added to the schedule of assessments to allow evaluation of clinical remission.
- The use of steroid injections during the first 8 weeks of blinded treatment was prohibited
- All patients were required to receive oral folate at a dose of at least 5 mg/week as part of the study inclusion criteria.
- The exclusion criteria which stated patients were to be excluded if they had granulomatous disease on chest X-ray was modified to say patients were to be excluded if they had evidence of 'clinically significant abnormalities' on chest X-ray. This ensured patients who had evidence of a granuloma, which in the opinion of the investigator, was not clinically significant, could participate in the study (providing they fulfilled all other criteria)
- Added further clarification to the exclusion criterion for history of malignancies
- Added that patients could be re-screened on one occasion
- Added additional follow-up visits 8 & 12 weeks after the last infusion of study treatment for patients who had not enrolled into the transition phase or long-term extension study
- Added collection of red blood cell (RBC) data, where necessary, and to express reticulocyte levels as an absolute count
- Added definition of when worsening of RA should be recorded as an adverse event
- Added an additional secondary endpoint to determine the proportion of patients who achieved a remission according to the ACR remission criteria at Week 24.
- Clarified that DAS28 and not DAS would be used in the assessment of remission
- Added clarification that the CRF served as the source document for assessments of questionnaires, VAS and joint counts.
- Added chloroquine and mycophenolic acid sodium to the list of prohibited medications.

2. Second Amendment – Protocol Version C, was dated October 3, 2006 (at which point all patients were enrolled) introduced the following changes:

- Added guidance for investigators regarding 1) the association of gastrointestinal perforation in patients with a history of gastrointestinal disorders and concurrent corticosteroid and/or NSAID treatment, and 2) the need to assess these patients for possible prophylactic treatment with proton pump inhibitors.
- The sampling strategy to test for anti-tocilizumab antibodies during the core study and transition phase was modified. After study completion, patients who tested positive for anti-tocilizumab antibodies were tested at additional time points throughout the study to fully evaluate the time of antibody formation.

Protocol Violations

The number of major protocol violations requiring study withdrawal was small: only two patients in the placebo controlled substudy. The proportion of patients excluded from the Per-Protocol population, which was the primary analysis population, was approximately 8% in both treatment groups. Of the deviations resulting in exclusion from the Per-Protocol analysis population, inclusion/exclusion criteria violations were the most common, ranging from 6% of patients in the MTX monotherapy group to 4% of the patients enrolled into the TCZ 8 mg/kg monotherapy group. The number of patients experiencing deviations that could possibly affect the Week 24 primary endpoint assessment was very low overall and deviations were distributed similarly among the treatment groups. Therefore these protocol deviations are unlikely to have biased the results of the primary efficacy analysis or compromised the overall integrity of the study data.

Table A-66 Protocol Deviations for Study WA17824

Protocol Deviations for Study WA17824 (Safety Population)		
	MTX[a]	TCZ 8 mg/kg[b]
	n (%)	n (%)
Enrolled	284	288
Met requirements for Per Protocol Pop	259 (91)	265 (92)
Excluded from Per Protocol Pop	25 (9)	23 (8)
Protocol violation resulting in withdrawal	-	-
Reasons pertaining to protocol violations (>1 may apply per patient)		
Inclusion/Exclusion criteria violations	16 (6)	11 (4)
Medication or randomization error	-	2
Change in corticosteroid within 2 weeks of Wk 24 assessment	2	1
Received change in NSAID dose within 2 wks of Wk 24	2	2
Received IM or IV corticosteroids	3	2
Joint counts not performed by independent assessor	-	1
Audit discrepancy or code break	4	5

a) includes 192 in main study and 92 in placebo substudy randomized to MTX
b) includes 200 in main study and 88 in placebo substudy randomized to TCZ 8 mg/kg
Source: Table 6 & 8 of WA17824 CSR

Patient disposition, baseline demographics, baseline disease characteristics have been discussed in conjunction with the 4 other pivotal studies in section 6.1.3 Demographics, and section 6.1.4 Patient Disposition, above. These conclusions apply to the individual study data for WA17823 reported here. To limit redundancy, results are presented in tabular format but will not be discussed in detail.

Table A-67 Patient Disposition for Study WA17824

Patient Disposition for Study WA17824 (Safety Population)			
	MTX[a] n (%)	TCZ 8 mg/kg[b] n (%)	Placebo x 8 wk f/b TCZ 8 mg/kg n (%)
Enrolled	284	288	101
Completed	262 (92)	268 (93)	82 (81)
Entered Escape*	11 (4)	7 (2)	14 (14)
Total discontinuations	22 (8)	20 (7)	19 (19)
Discontinuation due to AEs	11 (4)	9 (3)	5 (5)
SAEs (other than death)	3	2	0
Deaths	1	3	0
Other AE	7	4	5
Other withdrawals	11 (4)	11 (4)	14 (14)
Insufficient treatment effect	3	1	4
Protocol violation	0	0	2
Lost to follow-up	1	4	4
Patient choice	7	6	3
Other	0	0	1

* Escape available for placebo substudy patients only, prior to Week 8
a) includes 192 in main study and 92 in placebo substudy randomized to MTX
b) includes 200 in main study and 88 in placebo substudy randomized to TCZ 8 mg/kg
Derived from Figure 3, Tables 6, 72 and section 3.1.1 and 7.3 of WA 17824 CSR

Table A-68 Baseline Demographics for Study WA17824

Baseline Demographics for Study WA17824 (PP Population)		
	MTX n = 259 n (%)	TCZ 8 mg/kg n = 265 n (%)
Gender		
Female	211 (81)	219 (83)
Male	48 (19)	46 (17)
Age (years)		
mean	50.1	51.1
range	19 - 83	18 - 79
Height (cm)		
mean	163.0	162.3
range	138 - 195	130 - 191
Weight (kg)		
mean	72.6	73.4
range	40 - 131	41 - 150
Race		
White	188 (73)	187 (71)
Asian	20 (8)	22 (8)
Native American	21 (8)	27 (10)
Black	11 (4)	10 (4)
Other	19 (7)	19 (7)
Ethnicity		
Hispanic	72 (28)	82 (31)
Non-Hispanic	187 (72)	183 (69)

Adapted from Table 9 of the WA17824 CSR

Table A-69 Baseline Disease Characteristics for Study WA17824

Baseline Disease Characteristics for Study WA17824 (PP Population)		
	MTX n = 259 n (%)	TCZ 8 mg/kg n = 265 n (%)
Duration of RA (years)		
mean	6.3	6.4
range	0.2 - 49.6	0.1 - 44.7
Number prev. DMARDs or TNF inhibitors		
mean	1.1	1.2
range	0 - 7	0 - 7
Baseline RF		
negative	65 (25)	67 (25)
positive	194 (75)	198 (75)
DAS 28		
mean	6.8	6.8
range	3.7 - 8.8	3.6 - 9.1
Oral steroid use		
no	137 (53)	137 (52)
yes	122 (47)	128 (48)
MTX Naïve		
no	88 (34)	89 (34)
yes	171 (66)	176 (66)

Adapted from Table 10 of the WA17824 CSR

Table A-70 Baseline Disease Activity for Study WA17824

Baseline Disease Activity, ACR Core Variables for Study WA17824 (PP Population)		
	MTX n = 259	TCZ 8 mg/kg n = 265
Tender joint count		
mean	31.1	32.2
range	9 - 68	8 - 68
Swollen joint count		
mean	18.9	19.3
range	6 - 66	6 - 65
ESR (mm/hr)		
mean	48.9	49.9
range	1 - 140	3 - 142
CRP (mg/dL)		
mean	3.0	2.9
range	.03 - 22.7	.02 - 18.4
HAQ-DI		
mean	1.5	1.6
range	0 - 3	0 - 3
Pain VAS (100 mm)		
mean	61.3	59.2
range	0 - 101	0 - 100
Patient Global VAS (100 mm)		
mean	65.4	64.0
range	8 - 102	5 - 100
Physician Global VAS (100 mm)		
mean	63.2	63.2
range	13 - 96	15 - 100

Adapted from Table 12 of the WA17824 CSR

Efficacy Results

Results of the non-inferiority assessment for ACR50 and ACR70 responses were not displayed in Section 6. Integrated Review of Efficacy, although the primary analysis results for ACR20 responses were displayed in Table 11. Therefore the non-inferiority analysis results for ACR20/50/70 responses are summarized below, in Table A-71. For ACR50 and ACR70, as well as for ACR20, results for treatment with TCZ 8 mg/kg monotherapy were within the pre-specified non-inferiority margin of -0.12 (lower limit of 95% CI of TCZ minus MTX); therefore in each case, non-inferiority to MTX was demonstrated. The protocol pre-specified that in the event that non-inferiority to MTX was demonstrated, that a superiority assessment could be performed. The results of this analysis are summarized in Table 8 in the main body of this review. This analysis demonstrated that TCZ 8 mg/kg monotherapy was superior to MTX monotherapy, with 70% of patients achieving ACR20 responses in the TCZ monotherapy group compared to 52% of patients in the MTX monotherapy group. Results for ACR50 (TCZ 44%, MTX 34%) and ACR70 (TCZ 28%, MTX 15%) similarly supported the superiority of TCZ monotherapy over MTX monotherapy.

Table A-71 Non-inferiority Assessment, ACR20/50/70 responses, Study WA17824

Non-inferiority Assessment of the Difference in the Proportion of ACR Responders at Week 24 in Study WA17824 (Primary Analysis Population)		
	MTX n = 259 n (%)	TCZ 8 mg/kg n = 265 n (%)
ACR20		
Responders	135 (52)	187 (71)
Weighted difference vs. MTX		0.21
95% CI of weighted difference		(0.13, 0.29)*
ACR50		
Responders	85 (33)	115 (43)
Weighted difference vs. MTX		0.13
95% CI of weighted difference		(0.04, 0.21)
ACR70		
Responders	39 (15)	78 (28)
Weighted difference vs. MTX		0.14
95% CI of weighted difference		(0.06, 0.22)

* Non-inferiority demonstrated if lower limit of 95% CI of TCZ minus MTX >=-0.12
Primary analysis population, per-protocol
Adapted from Tables 16 and 21 of the WA17824 CSR

A proportion of patients at certain sites in the US, Canada, and Israel were randomized to a placebo-controlled substudy of WA17824, which served as an internal control. Results of this substudy are summarized in Table A-72 below. At Week 8 (the end of the placebo period), 41% of patients on TCZ 8 mg/kg monotherapy achieved an ACR20 response, compared to 13% of patients who were on placebo monotherapy. The 95% CI of the difference between TCZ and MTX excluded zero, providing additional evidence of the efficacy of TCZ in this study.

Table A-72 Results of Placebo-Controlled Substudy of Study WA17824

Assessment of the Difference in the Proportion of ACR20 Responders at Week 8 in Placebo-Controlled Substudy of Study WA17824 (ITT Population)		
	Placebo/MRA n = 99 n (%)	TCZ 8 mg/kg n = 86* n (%)
ACR20		
Responders	13 (13)	35 (41)
Weighted difference vs. MTX		0.28
95% CI of weighted difference		(0.16, 0.40)

*Includes only patients from the centers where the substudy was conducted
Statistical significance if lower limit of 95% CI of TCZ minus placebo >0
Analysis stratified by disease duration
Adapted from Table 19 of the WA17824 CSR

Safety Results
Refer to section 7 Integrated Review of Safety.

9.4.4 Study WA18062

9.4.4.1 WA18062 Study Protocol

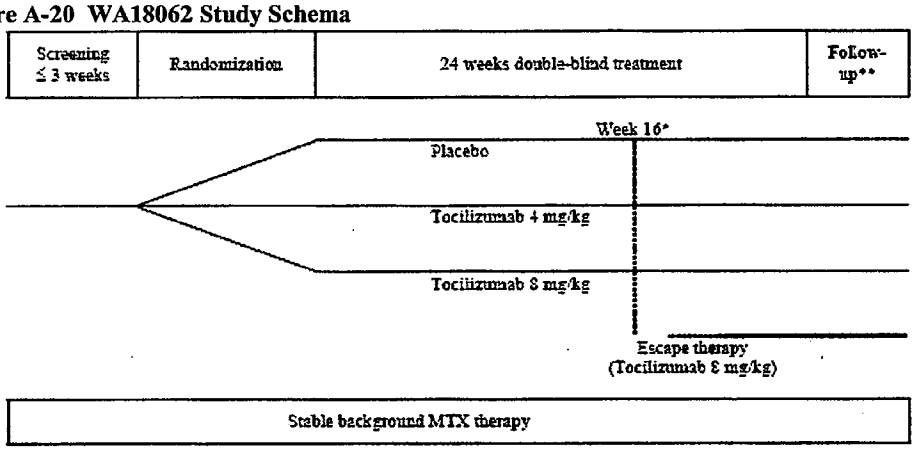
Overall Study Design

Study WA18062 is a 24-week randomized, double-blind, placebo-controlled study in 499 patients with moderately to severely active RA with previous inadequate clinical response to, or who were intolerant of, treatment with one or more TNF inhibitor therapies within one year prior to randomization. This study was conducted at 128 centers in 13 countries; 70 sites were in the US, and the total US patient population was 258 (52% of the total).

Patients were randomized (1:1:1) to 3 groups: TCZ 4 mg/kg IV every 4 weeks, TCZ 8 mg/kg IV every 4 weeks, or placebo IV every 4 weeks, given in addition to background treatment with MTX 10 to 25 mg (stable dose) weekly. Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy (TCZ 8 mg/kg + MTX) at weeks 16 and 20.

The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the week 24 visit, all patients (including escape patients) could roll-over into an open-label long-term extension study (WA18696) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years.

Figure A-20 WA18062 Study Schema



* Patients who did not achieve a 20% improvement from baseline in both SJC and TJC at Week 16 could receive escape therapy (comprising tocilizumab 8 mg/kg + MTX) at Weeks 16 and 20.

** Patients who did not enroll into a long-term extension study returned for safety follow-up assessments 8 and 12 weeks after the last infusion of study treatment.

Figure 1 of WA18062 CSR

Inclusion Criteria

Inclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol) except for the following:

1. Within 1 year prior to randomization, patients must have experienced an inadequate response to treatment with etanercept, infliximab, or adalimumab because of either inadequate efficacy or because of toxicity. (Minimum exposure for lack of efficacy: etanercept ≥3 months at 25 mg twice a week or 50 mg once weekly, at least 4 infusions of infliximab at ≥3 mg/kg, or adalimumab at minimum of 40 mg every other week for ≥3 months. Minimum exposure for toxicity, at least 1 complete dose.)

Exclusion Criteria

Exclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

Concomitant Medications

In addition to TCZ or placebo, all patients received MTX at a stable pre-entry dose of between 10 and 25 mg/week. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs were permitted during the study provided the dose was stable for at least 6 weeks prior to baseline. It was generally considered as standard of care that patients who received corticosteroids and/or NSAIDs also receive prophylactic treatment with proton pump inhibitors at a recommended dose or H_2-receptor blockers at a

maximum recommended dose. Patients on the study were to be assessed and prophylactic treatment added according to the investigator's discretion and local standards of care. The October 2006 protocol amendment required investigators to assess patients taking corticosteroids and/or NSAIDs, and where appropriate, institute GI prophylaxis with a proton pump inhibitor

Immunization with a live or attenuated vaccine was prohibited within 4 weeks prior to baseline and for the duration of study participation, including the 12 week follow-up period after administration of the last dose of infused study medication.

MTX: Dose reductions of MTX or a change of route of administration could be made at any time for safety reasons.

NSAIDs (including COX-2 inhibitors) were allowed throughout the study, up to their maximum recommended dose. The choice and dose of NSAIDs was at the discretion of the investigator. Alterations in NSAID dose were strongly discouraged for the first 24 weeks of the study. Dose adjustments were permitted for safety reasons and, if absolutely required, to treat disease flares. Aspirin (maximum 350 mg/day) was allowed to reduce cardiovascular risk.

Oral corticosteroids: Alterations in background oral corticosteroid dose were strongly discouraged for the first 24 weeks of the study. To treat non-RA conditions, such as asthma, increased doses of oral corticosteroids, up to 40 mg of prednisone daily (or equivalent) for 2 weeks or less was permitted. The corticosteroid dose was to be tapered down to the previous level as rapidly as medically possible.

Intravenous, intramuscular or intra-articular corticosteroids: Treatment with intravenous or intramuscular corticosteroids was not permitted during the study. Similarly, the use of intra-articular corticosteroids was not permitted within 6 weeks prior to baseline. Injection of intra-articular corticosteroids while on blinded study treatment also was discouraged, but was allowed to a limited extent. No more than one joint was to be injected and no single injection was to exceed 40 mg of triamcinolone (or equivalent).

Analgesics (other than NSAIDs): Analgesics up to their maximum recommended doses were allowed for pain management, as needed. However, analgesics were to be avoided within 24 hours prior to a visit where clinical efficacy assessments were performed and recorded.

Folic acid: In order to minimize MTX toxicity, all patients were to receive a stable dose of ≥ 5 mg/week folate (or equivalent) given, at the investigator's discretion, as either a single dose or as divided daily doses.

All DMARDs and non-biologic DMARDs other than the study treatments were prohibited.

Assignment to treatment group

Approximately 450 patients were to be randomly assigned in an equal manner to one of three treatment groups: tocilizumab 8 mg/kg + MTX, tocilizumab 4 mg/kg + MTX, or placebo + MTX.

Randomization was assigned centrally via an interactive voice response system (IVRS) and was stratified by site using a randomization list provided by Roche. A patient's eligibility was evaluated by the investigator to ensure that the inclusion and exclusion criteria were met and that the patient was eligible for participation in the study. Eligible patients were then randomized and assigned a unique randomization number. Medication numbers were assigned by the IVRS prior to dosing at each dosing visit depending on the patient's weight and allocated treatment arm in order to ensure that the correct dosage was provided.

Blinding

This was a blinded study, with the sponsor, investigators, and patients unaware of the treatment assignment of each patient. Study medication was administered as double dummy in order to maintain the blind. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment.

In order to maintain the double-blind status of the study, once infused study treatment had commenced, acute phase reactant data from the central laboratory were blinded to site and sponsor personnel. Results of the PK assays were also not available to the investigators and were blinded to the sponsor and monitors during the course of the study.

Drug Administration

Same as for Study WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

Criteria for Withdrawal from Treatment or Study and Replacement Policy

Same as for Study WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

Dose Modification

Same as for Study WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

Infusion Reactions

Same as for WA17822.

Schedule of Assessments

Table A-73 Schedule of Assessments for Study WA18062

	Week (± 3 days)												
	-3* SC	0* BL	2	4	6	8	12	14	16	20	24 WD 1	28 WD 2	32 WD 3
Informed consent	x												
Demographics	x												
Medical history	x	x[1]											
Inclusion/exclusion	x	x											
Pregnancy test (urine)[2]	x	x		x		x	x		x	x	x		
Physical examination	x										x		
Vital signs, weight	x	x[3]		x[3]		x[3]	x[3]		x[3]	x[3]	x	x	x
Study drug infusion[4]		x		x		x	x		x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x[5]										x		
Chest radiograph	x												
Efficacy													
Joint counts	x	x	x	x		x	x		x	x	x		
PT/INV global		x	x	x		x	x		x	x	x		
Pain VAS		x	x	x		x	x		x	x	x		
HAQ-DI		x	x	x		x	x		x	x	x		
FACIT-Fatigue		x		x		x	x		x	x	x		
SF-36		x				x			x		x		
MRU		x		x		x	x		x	x	x		
High sensitivity CRP	x	x	x	x	x	x	x	x	x	x	x		
ESR	x	x	x	x	x	x	x	x	x	x	x		
SAA		x	x	x	x	x	x	x	x	x	x		
Serum ferritin		x	x	x	x	x	x	x	x	x	x		
Haptoglobin		x	x	x	x	x	x	x	x	x	x		
Safety													
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x
Hematology (CBC)	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood chemistry (including LFTs)	x	x[6,7]	x	x	x[7]	x	x	x[7]	x	x	x[7]	x[7]	x[7]
Lipid panel	x[5]	x[7]			x[7]			x[7]			x[7]	x[7]	x[7]
Urinalysis	x	x		x		x			x		x	x	x
Hemolysis profile[9]		x									x		
General immunology													
RF	x	x									x	x	x

Table A-73 Schedule of Assessments for Study 18062 (continued)

	Week (± 3 days)												
	-3* SC	0* BL	2	4	6	8	12	14	16	20	24 WD 1	28 WD 2	32 WD 3
ANA (if pos.: anti-dsDNA)		x							x		x	x	x
Quantitative Ig		x									x	x	x
Complement (C3, C4)		x							x		x	x	x
PK/PD samples including tocilizumab, IL-6, sIL-6R, anti-tocilizumab and biomarkers[10]													
			All patients[11]										
Tocilizumab[12]		x[13]	x[14]	x[14]	x[14]	x[14]	x[13]	x[14]	x[14]	x[13]	x[13]		
IL-6[12]		x[13]	x[14]	x[14]	x[14]	x[14]	x[13]	x[14]	x[14]	x[13]	x[13]		
sIL-6R[12]		x[13]	x[14]	x[14]	x[14]	x[14]	x[13]	x[14]	x[14]	x[13]	x[13]		
Anti-tocilizumab antibodies (2 aliquots)[12]		x[13]	x[15]	x[15]	x[15]	x[15]	x[13]	x[15]	x[15]	x[15]	x[13]		
			Additional sample for subgroup of patients[16]										
Post-dose tocilizumab[17]		x		x			x						
			Biomarker sample for storage[18]										
Serum[12]		x							x		x		
Blood (in PAXgene tubes for mRNA)[12]		x							x		x		

ANA = anti-nuclear antibodies, CBC = complete blood count, ECG = electrocardiogram, FACIT = Functional Assessment of Chronic Illness Therapy, HAQ-DI = Health Assessment Questionnaire Disability Index, LFT = liver function test, mRNA = messenger ribonucleic acid, MRU = medical resource utilization, RF = rheumatoid factor, SAA = serum amyloid A, SF-36 = sIL-6R = soluble IL-6 receptor, VAS = visual analogue scale, WD = Withdrawal visit – assessments were performed at the time of premature withdrawal.

*The screening visit (SC) could occur up to 3 weeks prior to the first dose of double-blind study treatment and the baseline visit (BL) and randomization could occur up to 3 days prior to the first dose of double-blind study treatment.

1. Included in Medical History, and recorded in the CRF at baseline: the presence or absence of fibromyalgia and coronary heart disease risk factors
2. Pregnancy tests were conducted for female patients of childbearing potential
3. Vital signs were to be taken pre-dose and every 30 minutes during and 30 minutes after the infusion
4. Tocilizumab/placebo infusion could be administered up to 3 days after the study visit at which the protocol-designated study assessments were conducted
5. At the screening visit, two ECGs were taken at least 2 minutes apart
6. If ALT, AST, or bilirubin were > 2 x ULN, a liver function profile was performed
7. Overnight fasting
8. Non-fasted triglycerides only
9. To be performed at baseline and Week 24 and if bilirubin was elevated during the study
10. All samples were taken from a single blood draw and aliquoted according to the aliquoting procedures in the laboratory manual
11. All samples were taken from a single blood draw. Samples were then either analyzed or stored depending on the visit and whether they had consented to participate as part of the 10% of the population undergoing population PK
12. Samples were to be taken pre-dose on dosing days
13. Sample was to be analyzed in all patients
14. Sample was to be analyzed in 10% of the population who had consented to additional PK, and stored for all other patients for potential analysis on a case-by-case basis
15. Sample was to be stored for all patients
16. Samples were to be taken in approximately 10% of the population who had consented to participate in the additional PK
17. Sample was to be taken within 15 minutes following completion of the infusion
18. Samples were to be taken only in patients who had consented to a sample being taken and stored for biomarker analysis

Note: On dosing days, blood samples for routine safety, immunology, and storage were to be taken pre-dose.

Table 1 of WA18062 CSR

Table A-74 Schedule of Assessments for Patients on Escape Therapy, Study WA18062

	Week (± 3 days)						
	16	18	20	22	24 WD 1	28 WD 2	32 WD 3
Pregnancy test (urine)[2]	x		x		x		
Physical examination					x		
Vital signs, weight	x[2]		x[2]		x	x	x
Study drug infusion[3]	x		x				
Concomitant medications	x	x	x	x	x	x	x
ECG					x		
Efficacy							
Joint counts	x	x	x		x		
PT/INV global	x	x	x		x		
Pain VAS	x	x	x		x		
HAQ	x	x	x		x		
FACIT-fatigue	x		x		x		
SF-36	x				x		
MRU	x		x		x		
High sensitivity CRP	x	x	x	x	x		
ESR	x	x	x	x	x		
SAA	x	x	x	x	x		
Serum ferritin	x	x	x	x	x		
Haptoglobin	x	x	x	x	x		
Safety							
Adverse events	x	x	x	x	x	x	x
Hematology (CBC)	x	x	x	x	x	x	x
Blood chemistry (including LFTs)[4]	x	x	x	x[5]	x[5]	x[5]	x[5]
Lipid panel				x[5]	x[5]	x[5]	x[5]
Urinalysis	x				x	x	x
Hemolysis profile[6]					x		
General immunology							
RF					x	x	x
ANA (if pos.: anti-dsDNA)	x				x	x	x
Quantitative Ig					x	x	x
Complement (C3, C4)	x				x	x	x

Table A-74 Schedule of Assessments for Patients on Escape Therapy, Study 18062 (continued)

	Week (± 3 days)						
	16	18	20	22	24 WD 1	28 WD 2	32 WD 3
PK/PD samples including tocilizumab, IL-6, sIL-6R, anti-tocilizumab, and biomarkers							
	All patients						
Tocilizumab[7]	x[8]	x[8]	x[9]	x[8]	x[10]		
IL-6[7]	x[8]	x[8]	x[9]	x[8]	x[10]		
sIL-6R[7]	x[8]	x[8]	x[9]	x[8]	x[10]		
Anti-tocilizumab antibodies (2 aliquots)[7]	x[9]	x[9]	x[9]	x[9]	x[10]		
	Biomarker sample for storage[11]						
Serum[7]	x				x		
Blood (in PAXgene tubes for mRNA)[7]	x				x		

HAQ = Health Assessment Questionnaire
Visits could be performed ± 3 days.
1. Pregnancy tests were conducted for female patients of childbearing potential
2. Vital signs were to be taken pre-dose and every 30 minutes during and 30 minutes after the infusion
3. Tocilizumab/placebo infusion could be administered up to 3 days after the study visit at which the protocol-designated study assessments were conducted
4. If ALT, AST, or bilirubin were > 2 x ULN, a liver function profile was performed
5. Overnight fasting
6. To be performed at baseline and Weeks 24 and 28 and if bilirubin was elevated during the study
7. Samples were to be taken pre-dose on dosing days
8. Sample was to be analyzed in 10% of the population who had consented to additional PK, and stored for all other patients for potential analysis on a case-by-case basis
9. Sample was to be stored for all patients
10. Sample was to be analyzed in all patients
11. Samples were to be taken only in patients who had consented to a sample being taken and stored for biomarker analysis

Note: On dosing days, blood samples for routine safety, immunology, and storage were to be taken pre-dose.

Table 2 of WA18062 CSR

Efficacy Parameters

Efficacy parameters were the same as for WA17822 and are discussed above in section 9.4.1.1 WA17822 Study Protocol.

The primary and secondary endpoints, their analytical approaches and how missing data were imputed for them (pre-specified in the statistical analysis plan) are described in Tables A-48 and A-49 above, excerpted from the statistical review by Dr. Joan Buenconsejo. These endpoints were common to all the studies. Study WA18062 did not have any additional endpoints to these.

9.4.4.2 WA18062 Study Conduct

Study dates 5-27-05 to 4-18-07.

Protocol Amendments

Three protocol amendments were implemented during the conduct of the study. A list of major protocol changes are given below.

1. First Amendment – Protocol Version B, dated January 2006, was finalized but never submitted to an investigator or Institutional Review Board (IRB)/Independent Ethics Committee (IEC). After additional sponsor review of Protocol Amendment B, it was found that there was an omission in an assessment table. Subsequently, Protocol Amendment C was completed and included all of the items in Protocol Amendment B and the revised assessment table.

2. Second Amendment – Protocol Version C, dated January 2006, occurred when the vast majority of patients had already been recruited into the study, and introduced the following changes:

- Specified that patients could be re-screened once
- Clarified, in inclusion criterion 4, that the minimum treatment requirement for determining that a patient had failed an anti-TNF agent due to toxicity was at least 1 complete dose
- Clarified in exclusion criterion 1 that planned major surgery within 6 months following randomization would exclude a patient from the study
- Modified exclusion criterion 16 to exclude 'clinically significant abnormalities on chest X-ray as determined by the investigator' rather than specifying 'granulomatous disease on chest X-ray'
- Added further clarification for exclusion criterion 18 (history of malignancies)
- The sample size was reduced from 570 patients to 450, which allowed for earlier completion of enrollment with a power of 80% for the statistical analyses
- Clarified the list of prohibited medications and that treatments for RA include folic acid
- Clarified that joint assessments should be carried out by the same joint assessor for all study visits, whenever possible, and that the physician's global assessment of disease activity should be performed by the treating physician
- Specified that the infusion bag of tocilizumab or tocilizumab placebo may be stored for no longer than 6 hours at room temperature
- Updated the laboratory tests and procedures section to include red blood cell (RBC) at the central or local laboratory where the hemolysis profile is recorded, to eliminate routine hemolysis profiles from follow-up visits (Weeks 28 and 32), to eliminate the Week 24 chest x-ray, and to add collection of adverse event reports at Week 32
- Clarified when worsening of RA constituted an adverse event
- Clarified that patients who did not receive tocilizumab in a long-term extension study were to return for safety follow-up visits

3. Third Amendment – Protocol Version D, dated October 2006, occurred when all patients were recruited into the study and introduced the following changes:

- Added guidance for investigators regarding 1) the association of gastrointestinal perforation in patients with a history of gastrointestinal disorders and concurrent corticosteroid and/or NSAID treatment, and 2) the need to assess these patients for possible prophylactic treatment with proton pump inhibitors.
- Abatacept, which had been approved by the United States Food and Drug Administration following finalization of the protocol, was added to the list of prohibited medications
- The testing strategy for patients who were positive for anti-tocilizumab antibodies was updated
- Clarified that a hemolysis profile was also to be performed at Week 28 in addition to baseline and Week 24 if bilirubin was elevated during the study

Protocol Violations

The number of major protocol violations requiring study withdrawal was small: two patients in each of the TCZ treatment groups. The proportion of patients excluded from the Per-Protocol population was similar, at 27-33%. Of the deviations resulting in exclusion from the Per-Protocol analysis population, inclusion/exclusion criteria violations were the most common, ranging from 18% in the TCZ 8 mg/kg + MTX group to 26% in the TCZ 4 mg/kg + MTX group. The number of patients experiencing deviations that could possibly affect the Week 24 primary endpoint assessment was very low overall and deviations were distributed similarly among the treatment groups. Therefore these protocol deviations are unlikely to have biased the results of the primary efficacy analysis or compromised the overall integrity of the study data.

Table A-75 Protocol Deviations for Study WA18062

Protocol Deviations for Study WA18062 (ITT Population)			
	Placebo + MTX n (%)	TCZ 4mg/kg + MTX n (%)	TCZ 8 mg/kg + MTX n (%)
Enrolled	160	163	175
Met requirements for Per Protocol Pop	111 (69)	109 (67)	127 (73)
Excluded from Per Protocol Pop	49 (31)	54 (33)	48 (27)
Protocol violation resulting in withdrawal	-	2	2
Reasons for exclusion pertaining to protocol violations (more than one may apply per patient)			
Inclusion/Exclusion criteria violations	32 (20)	42 (26)	31 (18)
Medication or randomization error	3	1	4
Error in concomitant MTX administration	2	2	11
Change in corticosteroid within 4 weeks of Wk 24 assessment	4	3	2
Received change in NSAID dose within 2 wks of Wk 24	0	2	1
Received intra-articular steroids in violation of protocol specification	5	6	1
Received IM or IV corticosteroids	4	9	3
Joint counts not performed by independent assessor	1	1	1
Audit findings or code breaks	4	3	4

Source: Table 5 & 8 of WA18062 CSR

Patient disposition, baseline demographics, baseline disease characteristics have been discussed in conjunction with the 4 other pivotal studies in section 6.1.3 Demographics, and section 6.1.4 Patient Disposition, above. These conclusions apply to the individual study data for WA18063 reported here. To limit redundancy, results are presented in tabular format but will not be discussed in detail.

Table A-76 Patient Disposition for Study WA18062

Patient Disposition for Study WA18062 (ITT Population)			
	Placebo + MTX n (%)	TCZ 4mg/kg + MTX n (%)	TCZ 8 mg/kg + MTX n (%)
Enrolled	160	163	175
Randomized and treated*	158	161	170
Completed	127 (80)	138 (86)	152 (89)
Entered Escape	66 (42)	31 (19)	20 (12)
Total discontinuations	33 (20)	25 (15)	23 (13)
Discontinuation due to AEs	10 (6)	10 (6)	11 (6)
SAEs (other than death)	5	2	3
Deaths	0	0	0
Other AE	5	8	8
Other withdrawals	23 (14)	15 (9)	12 (7)
Insufficient treatment effect	19	6	4
Protocol violation	0	2	2
Lost to follow-up	0	4	1
Patient choice	4	2	4
Other	0	1	1

* ITT population
Derived from Figure 2, Tables 5 and 6 and pg. 192 of WA18062 CSR

Table A-77 Baseline Demographics for Study WA18062

Baseline Demographics for Study WA18062 (ITT Population)			
	Placebo + MTX n = 158 n (%)	TCZ 4mg/kg + MTX n = 161 n (%)	TCZ 8 mg/kg + MTX n = 170 n (%)
Gender			
Female	125 (79)	130 (81)	143 (84)
Male	33 (21)	31 (19)	27 (16)
Age (years)			
mean	53.4	50.9	53.9
range	20 - 83	19 - 78	21 - 82
Height (cm)			
mean	164.8	165.0	164.1
range	142 - 187	147 - 191	141 - 188
Weight (kg)			
mean	75.4	76.4	74.3
range	43 - 145	45 - 143	43 - 140
Race			
White	150 (95)	144 (89)	152 (89)
Asian	1 (<1)	4 (2)	5 (3)
Native American	2 (1)	3 (2)	1 (<1)
Black	3 (2)	10 (6)	7 (4)
Other	2 (1)	n/a	5 (3)
Ethnicity			
Hispanic	17 (11)	22 (14)	23 (14)
Non-Hispanic	140 (89)	139 (86)	146 (86)
Not known	1 (<1)	n/a	1 (<1)

Adapted from Table 10 of the WA18062 CSR

Table A-78 Baseline Disease Characteristics for Study WA18062

Baseline Disease Characteristics for Study WA18062 (ITT Population)			
	Placebo + MTX n = 158 n (%)	TCZ 4mg/kg + MTX n = 161 n (%)	TCZ 8 mg/kg + MTX n = 170 n (%)
Duration of RA (years)			
mean	11.4	11.0	12.6
range	0.8 - 53.3	0.9 - 46.6	0.8 - 62.0
Number previous TNF inhib.			
one	67 (42)	75 (47)	85 (50)
two	69 (44)	66 (41)	55 (32)
3 or more	22 (14)	20 (12)	30 (18)
Number previous DMARDs			
mean	2.1	2.0	1.9
range	0 - 7	0 - 6	0 - 7
Baseline RF			
negative	40 (25)	44 (27)	36 (21)
positive	118 (75)	117 (73)	134 (79)
DAS 28			
mean	6.8	6.8	6.8
range	3.6 - 8.9	4.3 - 8.8	4.6 - 8.7
Oral steroid use			
no	67 (42)	67 (42)	82 (48)
yes	91 (58)	94 (58)	88 (52)
Baseline MTX dose (mg/wk)			
mean	16.5	16.2	15.7
range	3 - 25	8 - 25	10 - 25
Time of discontinuation of previous TNF inhib. (days)			
mean	128	124	126
range	14 - 1705	14 - 1117	17 - 896

Adapted from Table 11 of the WA18062 CSR

Table A-79 Baseline Disease Activity for Study WA18062

Baseline Disease Activity, ACR Core Response Variables for Study WA18062 (ITT Population)			
	Placebo + MTX n = 158	TCZ 4mg/kg + MTX n = 161	TCZ 8 mg/kg + MTX n = 170
Tender joint count			
mean	30.4	31.3	31.7
range	5 - 68	8 - 68	8 - 67
Swollen joint count			
mean	18.9	19.5	18.9
range	4 - 50	6 - 52	6 - 56
ESR (mm/hr)			
mean	54.6	51.3	49.1
range	9 - 186	11 - 140	5 - 133
CRP (mg/dL)			
mean	3.7	3.1	2.8
range	.02 - 24.1	.02 - 18.1	.02 - 18.5
HAQ-DI			
mean	1.7	1.7	1.7
range	0 - 3	0 - 3	0 - 3
Pain VAS (100 mm)			
mean	64.1	63.5	64.7
range	0 - 100	0 - 100	18 - 100
Patient Global VAS (100 mm)			
mean	70.9	70.4	70.2
range	0 - 100	0 - 100	18 - 100
Physician Global VAS (100 mm)			
mean	67.5	66.5	66.4
range	22 - 100	20 - 100	14 - 100

Adapted from Table 13 of the WA18062 CSR

Efficacy Results

Refer to Section 6. Integrated Review of Efficacy, which contains the individual study results for WA18062 and each of the pivotal studies.

Safety Results
Refer to section 7 Integrated Review of Safety.

9.4.5 Study WA18063

9.4.5.1 WA18063 Study Protocol

Overall Study Design

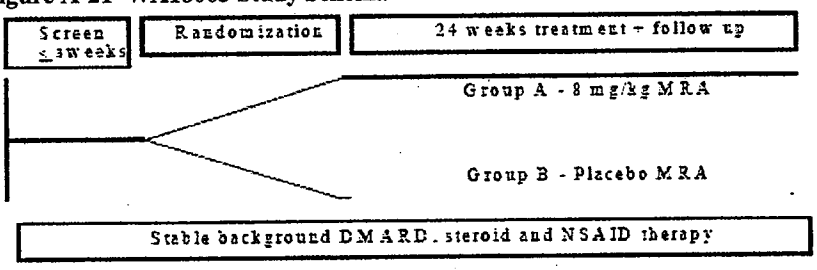
Study WA18063 is a 24-week randomized, double-blind, placebo-controlled study in 1220 patients with moderately to severely active RA with previous inadequate clinical response to current non-biologic DMARDs, including MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide. This

study was conducted at 130 centers in 18 countries; 64 sites were in the US, and the total US patient population was 498 (41% of the total).

Patients were randomized (2:1) to receive TCZ 8 mg/kg IV every 4 weeks or placebo IV every 4 weeks, in addition to background treatment with their current DMARD(s). Stable NSAIDs and corticosteroids (≤10 mg/day prednisone equivalent) were allowed to continue throughout the study. Patients who did not achieve a 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 16 could receive escape therapy (TCZ 8 mg/kg + MTX) at weeks 16 and 20.

The primary endpoint was the proportion of ACR20 responders at Week 24. Patients withdrawing or entering escape were considered non-responders for the primary efficacy analysis. After completion of the week 24 visit, all patients (including escape patients) could roll-over into an open-label long-term extension study (WA18696) and receive TCZ 8 mg/kg every 4 weeks for up to 5 years

Figure A-21 WA18063 Study Schema



Patients who did not achieve a 20% improvement from baseline in both swollen and tender joint counts at week 16 could receive escape therapy (comprising adjustment of background DMARD dose and/or treatment with a different traditional DMARD. Patients could also receive intraarticular steroids or an increase in their oral corticosteroid to a maximum dose of 10 mg daily) at weeks 16 and 20.
Patients who did not enroll into the long-term extension study, WA18696, returned for safety follow-up assessments 8 and 12 weeks after the last infusion of study treatment.
Figure 1 of WA18063 CSR

As noted in Figure A-21, patients who did not achieve a 20% improvement from baseline in both SJC and TJC at week 16 could, if requested and deemed necessary by the investigator, receive escape therapy, comprising adjustment of the background DMARD dose and/or treatment with a different traditional DMARD. Patients could also receive intra-articular steroids or an increase in their oral corticosteroids to a maximum dose of 10 mg daily. These medication adjustments as escape therapy could be made only one time during the study. Study medication continued during escape therapy. The option to receive escape therapy after 16 weeks of double-blind study treatment was available only for patients who had received two scheduled consecutive doses of double-blind study

treatment at weeks 8 and 12. Patients who received escape therapy were considered nonresponders in the primary efficacy analysis at 24 weeks.

Patients who withdrew from the study prior to week 16 were not eligible to receive escape therapy or to enter the long term extension study.

Inclusion Criteria

Inclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol) except for the following:

1. Instead of being limited to MTX, patients were to have received permitted DMARDs, each at a stable dose, for at least 8 weeks prior to baseline.
2. Removal of criteria related to withdrawal of non-biologic DMARDs
3. Removal of criteria related to folate.

Exclusion Criteria

Exclusion criteria are the same as for WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

Concomitant Medications

In addition to TCZ or placebo, all patients continued permitted non-biologic DMARDs at a stable pre-entry dose. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs were permitted during the study provided the dose was stable for at least 6 weeks prior to baseline. It was generally considered as standard of care that patients who received corticosteroids and/or NSAIDs also receive prophylactic treatment with proton pump inhibitors at a recommended dose or H_2-receptor blockers at a maximum recommended dose. Patients on the study were to be assessed and prophylactic treatment added according to the investigator's discretion and local standards of care. The October 2006 protocol amendment required investigators to assess patients taking corticosteroids and/or NSAIDs, and where appropriate, institute GI prophylaxis with a proton pump inhibitor

Immunization with a live or attenuated vaccine was prohibited within 4 weeks prior to baseline and for the duration of study participation, including the 12 week follow-up period after administration of the last dose of infused study medication.

DMARDs: The following DMARDs were permitted for use in this study: MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide. These DMARDs could be used alone or in combination, except for the combination of MTX and leflunomide, which was not allowed. DMARD dose reductions or a change of route of administration could be performed at anytime for safety. If dose reduction was a result of intolerance, this was recorded as an adverse event and the dose

modification was recorded in the CRF. If the investigator then determined it to be in the patient's best interest to increase the dose, reintroducing the DMARD to the baseline dose was allowed. Escape therapy guidelines were followed for DMARD dose increases that exceeded the baseline dose.

NSAIDs (including COX-2 inhibitors) were allowed throughout the study, up to their maximum recommended dose. The choice and dose of NSAIDs was at the discretion of the investigator. Alterations in NSAID dose were strongly discouraged for the first 24 weeks of the study. Dose adjustments were permitted for safety reasons and, if absolutely required, to treat disease flares. Aspirin (maximum 350 mg/day) was allowed to reduce cardiovascular risk.

Oral corticosteroids: Alterations in background oral corticosteroid dose were strongly discouraged for the first 24 weeks of the study. To treat non-RA conditions, such as asthma, increased doses of oral corticosteroids, up to 40 mg of prednisone daily (or equivalent) for 2 weeks or less was permitted. The corticosteroid dose was to be tapered down to the previous level as rapidly as medically possible.

Intravenous, intramuscular or intra-articular corticosteroids: Treatment with intravenous or intramuscular corticosteroids was not permitted during the study. Similarly, the use of intra-articular corticosteroids was not permitted within 6 weeks prior to baseline. Injection of intra-articular corticosteroids while on blinded study treatment also was discouraged, but was allowed to a limited extent. No more than one joint was to be injected and no single injection was to exceed 40 mg of triamcinolone (or equivalent).

Analgesics (other than NSAIDs): Analgesics up to their maximum recommended doses were allowed for pain management, as needed. However, analgesics were to be avoided within 24 hours prior to a visit where clinical efficacy assessments were performed and recorded.

Folic acid: In order to minimize MTX toxicity, all patients were to receive a stable dose of ≥ 5 mg/week folate (or equivalent) given, at the investigator's discretion, as either a single dose or as divided daily doses.

All biologic DMARDs and non-biologic DMARDs other than the study treatments were prohibited.

Assignment to treatment group

Approximately 1200 patients were to be randomly assigned in a 2:1 ratio to 2 treatment groups: 800 patients to tocilizumab 8 mg/kg + DMARDs and 400 patients to placebo + DMARDs.

Randomization was administered centrally via an interactive voice response system

(IVRS) and was stratified by site using a randomization list provided by Roche. Patient eligibility was evaluated by the investigator to ensure that the inclusion and exclusion criteria were met and the patient was eligible for participation in the study. Eligible patients were then randomized and assigned a unique randomization number. In order to ensure the correct dosage was provided, prior to dosing, medication numbers were assigned by the IVRS according to the patient's weight and allocated treatment arm.

Blinding

This was a blinded study, with the sponsor, investigators, and patients unaware of the treatment assignment of each patient. Study medication was administered as double dummy in order to maintain the blind. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment.

In order to maintain the double-blind status of the study, once infused study treatment had commenced, acute phase reactant data from the central laboratory were blinded to site and sponsor personnel. Results of the PK assays were also not available to the investigators and were blinded to the sponsor and monitors during the course of the study.

Drug Administration

With respect to TCZ, same as for Study WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

All patients were to have received stable doses of permitted DMARDs for at least 8 weeks prior to baseline. Patients were to continue on this stable background DMARD dose. Background treatment doses could be modified for lack of therapeutic response or toxicity.

Criteria for Withdrawal from Treatment or Study and Replacement Policy

Same as for Study WA17822 (see section 9.4.1.1 WA17822 Study Protocol).

Dose Modification

Same as for Study WA17822 (see section 9.4.1.1 WA17822 Study Protocol). Detailed instructions for dose-modification, other than the scenarios under which this would be permitted, were not pre-specified for each of the individual permitted background DMARDs.

Infusion Reactions

Same as for WA17822.

Schedule of Assessments

Table A-80 Schedule of Assessments for Study WA18063

Week	-3[1] SCRN	0[1] BL	2 ±3d	4 ±3d	6 ±3d	8 ±3d	12 ±3d	14 ±3d	16 ±3d	20 ±3d	24 ±3d WD1	28 ±3d WD2	32 ±3d WD3
Informed consent	x												
Demographics	x												
Medical history	x	x[2]											
Inclusion/ exclusion	x	x											
Pregnancy Test (urine)[2]	x	x		x		x	x		x	x	x		
Physical examination	x										x		
Vital signs, weight	x	x[3]		x[3]		x[3]	x[3]		x[2]	x[2]	x	x	x
Study drug infusion		x		x		x	x		x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x[4]										x		
Chest radiograph	x												

Table A-80 Schedule of Assessments for Study WA18063 (continued)

Week	-3* SCRN	0* BL	2 ±3d	4 ±3d	6 ±3d	8 ±3d	12 ±3d	14 ±3d	16 ±3d	20 ±3d	24 ±3d WD1	28 ±3d WD2	32 ±3d WD3
Efficacy													
Joint counts	x	x	x	x		x	x		x	x	x		
PT/INV Global		x	x	x		x	x		x	x	x		
Pain VAS		x	x	x		x	x		x	x	x		
HAQ-DI		x	x	x		x	x		x	x	x		
Fatigue (FACIT-F)		x		x		x	x		x	x	x		
SF-36		x				x			x	x	x		
Medical resource utilization		x		x		x	x		x	x	x		
High sensitivity CRP	x	x	x	x	x	x	x	x	x	x	x		
ESR	x	x	x	x	x	x	x	x	x	x	x		
SAA (analyzed as safety parameter)		x	x	x	x	x	x	x	x	x	x		
Serum ferritin (analyzed as safety parameter)		x	x	x	x	x	x	x	x	x	x		
Haptoglobin (analyzed as safety parameter)		x	x	x	x	x	x	x	x	x	x		
Week	**-3* SCRN**	**0* BL**	**2 ±3d**	**4 ±3d**	**6 ±3d**	**8 ±3d**	**12 ±3d**	**14 ±3d**	**16 ±3d**	**20 ±3d**	**24 ±3d WD1**	**28 ±3d WD2**	**32 ±3d WD3**
Safety													
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x
Routine Labs													
Hematology (CBC)	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood chemistry (with LFTs)[5]	x	x[6]	x	x	x[6]	x	x	x[6]	x	x	x[6]	x[6]	x[6]
Hemolysis profile[7]		x									x	x	x
Liver function profile		x[6]											
Lipid panel	x[6]	x[6]			x[6]			x[6]			x[6]	x[6]	x[6]
Urinalysis	x	x		x		x			x		x	x	x

Table A-80 Schedule of Assessments for Study WA18063 (continued)

Week	-3* SCRN	0* BL	2 ±3d	4 ±3d	6 ±3d	8 ±3d	12 ±3d	14 ±3d	16 ±3d	20 ±3d	24 ±3d WD1	28 ±3d WD2	32 ±3d WD3
Immunology Labs													
Rheumatoid factor	x	x									x	x	x
ANA (if pos.: anti-dsDNA)		x							x		x	x	x
Quantitative Ig		x									x	x	x
Complement (C3, C4)		x							x		x	x	x
PK/PD samples including: tocilizumab, IL-6, IL-6R, anti-tocilizumab antibodies [9]													
All patients[10]													
Tocilizumab[11]		x[12]	x[13]	x[13]	x[13]	x[13]	x[12]	x[13]	x[13]	x[14]	x[12]		
IL-6[11]		x[12]	x[13]	x[13]	x[13]	x[13]	x[12]	x[13]	x[13]	x[14]	x[12]		
sIL-6R[11]		x[12]	x[13]	x[13]	x[13]	x[13]	x[12]	x[13]	x[13]	x[14]	x[12]		
Anti-tocilizumab antibodies (2 aliquots)[11]		x[12]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[12]		

Week	-3* SCRN	0* BL	2 ±3d	4 ±3d	6 ±3d	8 ±3d	12 ±3d	14 ±3d	16 ±3d	20 ±3d	24 ±3d WD1	28 ±3d WD2	32 ±3d WD3
Additional sample for subgroup of patients[15]													
Post-dose tocilizumab[16]		x		x			x						
Biomarker samples[17]													
Serum[11]		x							x		x		

WD = Withdrawal visits (assessments performed at the time of premature withdrawal from the study). WD1 assessments were to be performed 4 weeks after the last dose of study treatment; WD2 assessments were to be performed 8 weeks after the last dose of study treatment; and WD3 assessments were to be performed 12 weeks after the last dose of study treatment.

*The screening visit (SCRN) could occur up to 3 weeks prior to the first dose of double-blind study treatment and the baseline visit (BL) and randomization could occur up to 3 days prior to the first dose of double-blind study treatment.

1. Including presence or absence of fibromyalgia.
2. If of childbearing potential.
3. Vital signs were taken pre-dose and every 30 minutes during and 30 minutes after the infusion.
4. At screening, two ECGs were taken at least 2 minutes apart.
5. At baseline and weeks 6, 14, 24, and 32, serum insulin and C-peptide were assessed after patient fasted for 8 hours or more. If ALT, AST or bilirubin were > 2 times ULN, a liver function profile was performed.
6. Overnight fasting (> 8 hours).
7. To be performed at baseline and weeks 24, 28 and 32 and if bilirubin is elevated during the study.
8. At screening, non-fasted triglycerides only.
9. All samples (apart from the post dose sample) were taken from a single blood draw and aliquoted according to the laboratory manual procedures.
10. All samples were taken in all patients. Samples were then either analyzed or stored depending on the visit and whether the patient consented to participate in the additional PK sampling (20% of the study population).
11. Sample was taken pre-dose on dosing days.
12. Sample was analyzed in all patients.
13. Sample was analyzed in 20% of the population who consented to participate in additional post-dose PK sampling, and stored for all other patients for potential safety analysis on a case-by-case basis.
14. Sample was stored in all patients.
15. Approximately 20% of patients at selected centers who consented to participate in additional PK sampling.
16. Samples were taken within 15 minutes following completion of the infusion.
17. Samples were taken in only those patients who consented to a sample being taken and stored for biomarker analysis.

Note: study drug administration may have occurred within 3 days of the study assessments being performed.

Table 1 of WA18063 CSR

Efficacy Parameters

Efficacy parameters were the same as for WA17822 and are discussed above in section 9.4.1.1 WA17822 Study Protocol.

The primary and secondary endpoints, their analytical approaches and how missing data were imputed for them (pre-specified in the statistical analysis plan) are described in Tables A-48 and A-49 above, excerpted from the statistical review by Dr. Joan Buenconsejo. These endpoints were common to all the studies. Study WA18063 did not have any additional endpoints to these.

9.4.5.2 WA18063 Study Conduct

Study Dates 3-24-05 to 3-28-07.

Protocol Amendments

The protocol was amended twice. The first amendment occurred in February 2005, prior to patient enrollment in March 2005.

The second protocol amendment was implemented in October 2006, after patient enrollment was completed, but before many of the patients enrolled had reached week 24 in the study period. A list of major protocol changes is provided below:

- Added guidance for investigators regarding 1) the association of gastrointestinal perforation in patients with a history of gastrointestinal disorders and concurrent corticosteroid and/or NSAID treatment, and 2) the need to assess these patients for possible prophylactic treatment with proton pump inhibitors.
- Added the principal investigator;
- Refined the screening strategy/laboratory assessment time points for anti-tocilizumab antibodies;
- Corrected the methods and criteria for the Disease Activity Score 28 (DAS28) remission in the statistical analysis section, clarified use of DAS28, and provided a definition for "baseline";
- Revised the duration of the extension study from 36 months to 60 months;
- Clarified the safety analysis data set;
- Clarified that non-fasting triglycerides were to be taken at screening;
- Clarified that patients who have not received tocilizumab in the long-term extension study had to return for safety follow-up assessments at weeks 8 and 12 after the last infusion of study treatment; and
- Provided additional units of measurement for bilirubin and ANC.

Protocol Violations

The number of major protocol violations requiring study withdrawal was small: two patients in each of the TCZ treatment groups. The proportion of patients excluded from the Per-Protocol population was similar, at 27-33%. Of the deviations resulting in exclusion from the Per-Protocol analysis population, inclusion/exclusion criteria violations were the most common, ranging from 18% in the TCZ 8 mg/kg + MTX group to 26% in the TCZ 4 mg/kg + MTX group. The number of patients experiencing deviations that could possibly affect the Week 24 primary endpoint assessment was very low overall and deviations were distributed similarly among the treatment groups. Therefore these protocol deviations are unlikely to have biased the results of the primary efficacy analysis or compromised the overall integrity of the study data.

Table A-81 Protocol Deviations for Study WA18063

Protocol Deviations for Study WA18063 (ITT Population)		
	Placebo + DMARDs n (%)	TCZ 8 mg/kg + DMARDs n (%)
Enrolled	415[a]	805[b]
ITT Population	413	803
Met requirements for Per Protocol Pop	330 (80)	692 (86)
Excluded from Per Protocol Pop	85 (20)	112 (14)
Protocol violation resulting in withdrawal	3	-
Reasons pertaining to protocol violations (>1 may apply per patient)		
Inclusion/Exclusion criteria violations	26 (6)	49 (6)
Medication or randomization error	8	8
Error in concomitant treatment administration	11	18
Change in corticosteroid within 4 weeks of Wk 24 assessment	6	4
Received change in NSAID dose within 2 wks of Wk 24	1	1
Received intra-articular steroids in violation of protocol specification	8	7
Received IM or IV corticosteroids	11	16
Joint counts not performed by independent assessor	1	4
Blinding compromised due to code breaks	-	1

a) includes two patients randomized to group who were not dosed and two patients randomized to group but received TCZ 8 mg/kg throughout the study
b) includes two patients randomized to group who were not dosed and 3 who were randomized to group but received placebo throughout the study
Sources: Tables 5 & 7 of WA18063 CSR

Patient disposition, baseline demographics, baseline disease characteristics have been discussed in conjunction with the 4 other pivotal studies in section 6.1.3 Demographics,

and section 6.1.4 Patient Disposition, above. These conclusions apply to the individual study data for WA18063 reported here. To limit redundancy, results are presented in tabular format but will not be discussed in detail.

Table A-82 Patient Disposition for Study WA18063

Patient Disposition for Study WA18063 (ITT Population)		
	Placebo + DMARDs n (%)	TCZ 8 mg/kg + DMARDs n (%)
Enrolled	415[a]	805[b]
ITT Population	413	803
Completed	370 (90)	751 (94)
Entered Escape	45 (11)	19 (2)
Total discontinuations	43 (10)	53 (7)
Discontinuation due to AEs	8 (2)	32 (4)
SAEs (other than death)	3 (<1)	13 (2)
Deaths	2 (<1)	2 (<1)
Other AE	3 (<1)	17 (2)
Other withdrawals	35 (8)	21 (3)
Insufficient treatment effect	15 (4)	3 (<1)
Protocol violation	3 (<1)	0
Lost to follow-up	2 (<1)	2 (<1)
Patient choice	13 (3)	15 (2)
Other	2 (<1)	1 (<1)

a) includes two patients randomized to group who were not dosed and two patients randomized to group but received TCZ 8 mg/kg throughout the study

b) includes two patients randomized to group who were not dosed and 3 who were randomized to group but received placebo throughout the study

Derived from Figure 2 and Table 5 and sections 3.5.2.4 and of the 18063 CSR

Table A-83 Baseline Demographics for Study WA18063

Baseline Demographics for Study WA18063 (ITT Population)		
	Placebo+DMARD n = 413 n (%)	TCZ 8 mg/kg+DMARD n = 803 n (%)
Gender		
Female	346 (84)	654 (81)
Male	67 (16)	149 (19)
Age (years)		
mean	53.5	53.0
range	19 - 83	18 - 89
Height (cm)		
mean	163.0	162.9
range	141 - 196	130 - 198
Weight (kg)		
mean	73.3	74.0
range	36 - 139	36 - 138
Race		
White	297 (72)	580 (72)
Asian	41 (10)	76 (9)
Native American	35 (8)	84 (10)
Black	27 (7)	36 (4)
Other	13 (3)	27 (3)
Ethnicity		
Hispanic	97 (23)	206 (26)
Non-Hispanic	316 (77)	597 (74)

Adapted from Table 8 of the WA18063 CSR

Table A-84 Baseline Disease Characteristics for Study WA18063

Baseline Disease Characteristics for Study WA18063 (ITT Population)		
	Placebo+DMARD n = 413 n (%)	TCZ 8 mg/kg+DMARD n = 803 n (%)
Duration of RA (years)		
mean	9.8	9.8
range	0.5 - 44.4	0.4 - 46.1
Number previous TNF inhib. or other DMARDs		
mean	1.6	1.6
range	0 - 8	0 - 9
Baseline RF		
negative	102 (25)	179 (22)
positive	311 (75)	624 (78)
DAS 28		
mean	6.6	6.7
range	3.0 - 8.9	2.2 - 9.2
Oral steroid use		
no	186 (45)	393 (49)
yes	227 (55)	410 (51)
Number background DMARDs		
one	311 (75)	616 (77)
two	82 (20)	152 (19)
3 or more	15 (4)	26 (3)
none	5 (1)	9 (1)

Adapted from Table 9 of the WA18063 CSR

Table A-85 Baseline DMARD Use for Study WA18063

Baseline DMARD Use for Study WA18063 (ITT Population)		
	Placebo+DMARD n = 413 n (%)	TCZ 8 mg/kg+DMARD n = 803 n (%)
Baseline MTX (mg/wk)	304 (74)	609 (76)
mean	15.0	14.7
range	2.5 - 25	2.5 - 25
Baseline leflunomide (mg/d)	65 (16)	96 (12)
mean	18.4	18.9
range	8.6 - 20	8.6 - 30
Baseline sulfasalazine (mg/d)	58 (14)	106 (13)
mean	1948	1984
range	1000 - 4000	500 - 4000
Baseline azathioprine (mg/d)	9 (2)	18 (2)
mean	83.3	102.8
range	50 - 150	50 - 150
Baseline chloroquine (mg/wk)	27 (7)	48 (6)
mean	1318	1465
range	450 - 1750	500 - 3500
Baseline HCQ (mg/wk)	55 (13)	116 (14)
mean	2329	2338
range	700 - 4200	700 - 4200
Baseline parenteral gold (mg/wk)	3 (<1)	2 (<1)
mean	40.0	30.8
range	30 - 50	11.5 - 50

Adapted from Table 9 of the WA18063 CSR

Table A-86 Baseline Disease Activity for Study WA18063

Baseline Disease Activity, ACR Core Response Variables for Study WA18063 (ITT Population)		
	Placebo+DMARD n = 413 n (%)	TCZ 8 mg/kg+DMARD n = 803 n (%)
Tender joint count		
mean	29.1	30.1
range	2 - 68	6 - 68
Swollen joint count		
mean	18.7	19.7
range	1 - 63	2 - 66
ESR (mm/hr)		
mean	49.2	48.2
range	1 - 150	1 - 183
CRP (mg/dL)		
mean	2.6	2.6
range	.02 - 77.2	.02 - 37.2
HAQ-DI		
mean	1.5	1.5
range	0 - 3	0 - 3
Pain VAS (100 mm)		
mean	58.5	58.4
range	0 - 100	0 - 100
Patient Global VAS (100 mm)		
mean	66.5	66.2
range	2 - 100	0 - 100
Physician Global VAS (100 mm)		
mean	63.4	63.6
range	10 - 100	10 - 98

Adapted from Table 11 of the WA18063 CSR

Efficacy Results

Refer to Section 6. Integrated Review of Efficacy, which contains the individual study results for WA18063 and each of the pivotal studies.

Safety Results

Refer to section 7 Integrated Review of Safety.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125276/0 **Applicant: Hoffman-La Roche Stamp Date: 11-19-2007**

Drug Name: tocilizumab Actemra® **NDA Type: original submission**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			PLR format Includes Patient Info Sheet
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			In Module 2.7.4
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			In Module 2.7.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 6, Module 2.5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			Extensive dose ranging occurred in Chugai program; 3 of the pivotal trials submitted evaluated 4 mg/kg and 8 mg/kg
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Yes, 5 pivotal studies
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Japan and European trials submitted as supportive only
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Includes post-marketing data from Japan (Castleman's) and data from other indications under study
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			Yes—for 8 mg/kg, 3192 at least one dose; 2570 ≥6 months; 1443 ≥1 year
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?		X		A coding dictionary was not specifically requested of the sponsor at pre-BLA
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	First in class.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			Particular analyses were requested and provided
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Deferral for pJIA ages 2-17; waiver for ≤2 yo
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Foreign data, e.g. Japan and Europe, supportive only
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			WA17822, WA17823, WA17824, WA18062, WA18063
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No additional CRFs have been requested.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

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

1) Provide coding dictionary.

Sarah Okada, M.D. — Date: 12-11-07

Jeffrey N. Siegel, M.D. — Date: 12/11/07