

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> FOOD AND DRUG ADMINISTRATION  <b>APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b> <i>(Title 21, Code of Federal Regulations, Parts 314 &amp; 601)</i>		Form Approved: OMB No. 0910-0430 Expiration Date: April 30, 2009 See OMB Statement on page 2.
		<b>FOR FDA USE ONLY</b>
		APPLICATION NUMBER

<b>APPLICANT INFORMATION</b>		
NAME OF APPLICANT Hoffmann-La Roche Inc.	DATE OF SUBMISSION 07/02/2008	
TELEPHONE NO. (Include Area Code) (973) 562-2833	FACSIMILE (FAX) Number (Include Area Code) (973) 562-3700	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199 U.S.A.	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Matthew Lamb, Pharm.D. 340 Kingsland Street Nutley, New Jersey 07110-1199 U.S.A.	

<b>PRODUCT DESCRIPTION</b>		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 125276/0		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Tocilizumab	PROPRIETARY NAME (trade name) IF ANY ACTEMRA®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody		CODE NAME (If any) RO4877533
DOSAGE FORM: single-use vials	STRENGTHS: 80mg, 200mg, 400mg	ROUTE OF ADMINISTRATION: intravenous infusion
(PROPOSED) INDICATION(S) FOR USE: For the treatment of adult onset rheumatoid arthritis		

<b>APPLICATION DESCRIPTION</b>		
APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input checked="" type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
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REASON FOR SUBMISSION GENERAL CORRESPONDENCE: Briefing Package for the July 29, 2008 Arthritis Advisory Committee Meeting		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		
<b>ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)</b> Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
<b>Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)</b> BB-IND 11972, BB-IND 10045, BB-IND 10597, BB-IND 11475		

This application contains the following items: <i>(Check all that apply)</i>		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling <i>(check one)</i> <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
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<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
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<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER <i>(Specify)</i> Briefing Package for the July 29, 2008 Arthritis Advisory Committee Meeting	

**CERTIFICATION**

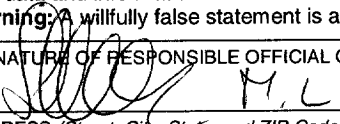
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Matthew Lamb, Pharm.D. Director, Global Reg Aff	DATE: 07/02/2008
ADDRESS <i>(Street, City, State, and ZIP Code)</i> 340 Kingsland Street, Nutley, New Jersey 07110-1199		Telephone Number ( 973 ) 562-2833

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July 1, 2008

Nicole Vesely, Pharm.D.  
Advisors and Consultants Staff  
FDA, CDER, OEP  
HFD-21, Room 1093  
5630 Fishers Lane  
Rockville, MD 20857-1734

**Re: BLA 125276 ACTEMRA® (tocilizumab, MRA, RO4877533)  
For the Treatment of Adult Onset Rheumatoid Arthritis  
GENERAL CORRESPONDENCE: ACTEMRA Briefing Package for the July 29, 2008 Arthritis  
Advisory Committee Meeting**

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Dear Dr. Vesely

Reference is made to Hoffmann-La Roche Inc.'s Biologics License Application (BLA), submitted under section 351 of the Public Health Service Act and in accordance with 21 CFR 601 supporting the use of ACTEMRA® for the treatment of patients with Adult Onset Rheumatoid Arthritis.

Reference is made to the letter from Dr. Nicole Vesely, dated April 7, 2008, which provides details on the Sponsor and FDA's briefing package for the July 29, 2008 Arthritis Advisory Committee Meeting which has been scheduled to discuss ACTEMRA (tocilizumab) for the proposed treatment of adult patients with moderately to severely active rheumatoid arthritis. As requested in your letter, 30 electronic CD copies and 12 paper copies of the Sponsor's background package, available for public disclosure, are included in this submission.

Should you have any questions concerning this submission, please feel free to contact the undersigned.

Sincerely,

**HOFFMANN-LA ROCHE INC.**



Matthew W. Lamb, Pharm.D.  
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Global Regulatory Affairs  
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SK/tc  
Attachments  
HLR No. N2008-01875

Desk copies: Ms. Sharon Turner-Rinehardt (3 copies)



**BRIEFING DOCUMENT FOR TOCILIZUMAB  
BIOLOGIC LICENSE APPLICATION 125276**

**FOOD AND DRUG ADMINISTRATION  
ARTHRITIS ADVISORY COMMITTEE  
JULY 29, 2008**

**Applicant:**

Hoffmann-LaRoche Inc

Nutley, NJ

**AVAILABLE FOR PUBLIC DISCLOSURE**

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## **GLOSSARY OF ABBREVIATIONS**

4MSU	Four-Month Safety Update
ACR	American College of Rheumatology
AUC	Area under the curve
BLA	Biologic Licensing Application
BSRBR	British Society for Rheumatology Biologics Registry
C <sub>min</sub>	Trough concentration
C <sub>max</sub>	Maximum concentration
CI	Confidence interval
CIA	Collagen induced arthritis
CL	Clearance
CRP	C-reactive protein
DAS	Disease activity score
DMARD	Disease modifying anti-rheumatic drug
DTH	Delayed type hypersensitivity
E <sub>max</sub>	Maximum Effect
EC <sub>50</sub>	Concentration at which 50% of the maximum effect is reached
ENTIS	European Network of Teratology Information Services
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
GI	Gastrointestinal
HAHAs	Human anti-human antibodies
HAQ-DI	Health Assessment Questionnaire Disability Index
HDL	High-density lipoprotein
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor

## **GLOSSARY OF ABBREVIATIONS**

IR	Inadequate Responders
ITT	Intent to treat
IV	Intravenous
LDL	Low-density lipoprotein
LLN	Lower limit of normal
mIL-6	Membrane bound IL-6
sIL-6	Soluble IL-6
MRA	Myeloma receptor antibody
MTX	methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PEB	Pharmacoepidemiology Board
pJIA	Polyarticular-course juvenile idiopathic arthritis
PP	Per protocol
RA	Rheumatoid arthritis
SAA	Serum amyloid A
SEER	Surveillance Epidemiology End Results
SF-36	Short form-36
SIR	Standardized incidence ratios
SJC	Swollen joint count
sJIA	Systemic juvenile idiopathic arthritis
TCZ	Tocilizumab
TJC	Tender joint count
TNF	Tumour necrosis factor
ULN	Upper limit of normal
V <sub>ss</sub>	Volume of distribution at steady state

## 1. EXECUTIVE SUMMARY

This document provides background information on the clinical development program for tocilizumab and summarizes the efficacy and safety data supporting its use in the treatment of rheumatoid arthritis (RA).

Actemra (tocilizumab; also known as myeloma receptor antibody [MRA]) is a recombinant humanized mouse anti-human interleukin-6 receptor (IL-6R) monoclonal antibody that binds specifically and with similar affinity to both soluble IL-6R (sIL-6R) and membrane-bound IL-6R (mIL-6R). Tocilizumab inhibits both sIL-6R- and mIL-6R-mediated signaling by preventing the binding of the IL-6/IL-6R complex to gp130 on cell surfaces.

The clinical development program evaluated the effects of tocilizumab on signs and symptoms of RA, physical function, and health-related quality of life in five pivotal clinical trials: three in patients with an inadequate response to disease modifying anti-rheumatic drugs (DMARDs), one in patients who failed anti-tumor necrosis factor (TNF) therapy, and one monotherapy study in patients with limited or no exposure to methotrexate (MTX). One of the five clinical studies continued for 2 years to assess both prevention of joint damage and improvement in physical function at 1 year (with confirmation at 2 years). Overall, 4211 patients were included in the clinical program and over 2500 patients have been followed in long-term extension studies.

Tocilizumab demonstrated robust and consistent efficacy in DMARD-inadequate and anti-TNF inadequate responders ([Table 1](#) and [Table 2](#), respectively).

**Table 1**      **Percentage of Patients with an ACR20, ACR50, and ACR70 Response at Week 24: DMARD-Inadequate Responders: 6-Month Pooled Data (ITT Population)**

Parameter	Placebo + DMARD (N=1010)	TCZ 4 mg/kg + MTX (N=612)	TCZ 8 mg/kg + MTX (N=1406)
ACR20	25.8%	49.7%	59.2%
ACR50	9.6%	27.3%	37.0%
ACR70	2.4%	11.4%	18.5%

MTX=methotrexate; TCZ=tocilizumab

All tocilizumab treatment groups were statistically superior to placebo at  $p < 0.0001$

Tocilizumab 8 mg/kg was statistically superior to 4 mg/kg at  $p < 0.05$

**Table 2**                      **Percentage of Patients with an ACR20, ACR50, and ACR70 Response at Week 24: Anti-TNF-Inadequate Responders (ITT Population)**

Parameter	Placebo + MTX (N=158)	TCZ 4 mg/kg + MTX (N=161)	TCZ 8 mg/kg + MTX (N=170)
ACR20	10.1%	30.4%	50.0%
ACR50	3.8%	16.8%	28.8%
ACR70	1.3%	5.0%	12.4%

All tocilizumab treatment groups were statistically superior to placebo at  $p < 0.0001$ , except for the 4 mg/kg group for ACR50 and ACR70

In the monotherapy study, tocilizumab 8 mg/kg (N=286) was statistically superior to MTX (N=284) with an ACR20 response of 69.9% versus 52.2%, respectively, an ACR50 response of 44.1% versus 33.5%, respectively, and an ACR70 response of 28.0% versus 15.1%, respectively ( $p < 0.001$  for all).

In the five pivotal Phase 3 studies, tocilizumab demonstrated consistent and robust effects on primary and key secondary endpoints in a broad range of RA patients with moderate to severe active RA whether they started DMARD therapy de novo or required additional treatment following an inadequate response to previous treatment. The data demonstrate that the 8 mg/kg dose offers the most reliable and consistent efficacy in all populations investigated and was the only dose that effectively controlled inflammation, as reflected by C-reactive protein (CRP), throughout the 10-month dosing interval. When treated with this dose, substantial numbers of patients achieved an ACR50 response, disease activity score (DAS28) remission, and a European League Against Rheumatism (EULAR) low disease activity or good response, which reflects clinically relevant improvements in signs and symptoms of the disease. Benefits were apparent at the first study visit (2 weeks) following the start of tocilizumab therapy and the magnitude of response was maintained with continued treatment for up to 2 years.

Tocilizumab was generally well tolerated. The safety profile was generally similar whether given as monotherapy or in combination with other non-biologic DMARDs. The proportion of patients withdrawing due to adverse events was similar in both the 4 mg/kg and 8mg/kg treatment groups.

In the monotherapy study, the incidence of serious infections was 1.50 events per 100 patient-years in the MTX group and 2.85 events per 100 patient-years in the tocilizumab group. In the pooled safety population, the rates of serious infections were 3.75 events per 100 patient-years in the placebo/DMARD group, 4.35 in the tocilizumab 4 mg/kg + DMARD group, and 5.18 in the tocilizumab 8 mg/kg + DMARD group and these rates did not increase over time. Opportunistic infections were observed in tocilizumab-treated patients in the controlled trials and the Total Safety Exposure group.

Overall, 13 patients (3 in the double-blind studies and 10 beyond 24 weeks; 4 mg/kg, 1 patient; 8 mg/kg, 12 patients) treated with tocilizumab and no patients in the comparator groups had gastrointestinal (GI) perforations. Two of the three upper GI



perforations were due to post-procedural complications. Nine of the 10 lower GI perforations were a consequence of diverticulitis.

In the double-blind studies, the rate of malignant neoplasms was 1.33 events per 100 patient-years and 1.27 in the tocilizumab and control groups, respectively. Following longer-term treatment, the rate in the total Phase 3 population was 1.45 events per 100 patient-years; excluding non-melanoma skin cancers, the rate was 0.91 per 100 patient-years. The risk of malignancy in patients receiving long-term treatment with tocilizumab is similar to the historical rates observed in RA patients receiving other immunosuppressive drugs.

Most ALT and AST elevations were transient and none of the elevations were associated with abnormal liver function. No serious adverse events were associated with the transaminase elevations during the clinical trials.

LDL levels were increased in both the 4 mg/kg and 8 mg/kg treatment groups and responded appropriately to statin therapy. Rates of myocardial infarction and stroke were similar across the tocilizumab and control treatment groups and did not increase over time.

The development of anti-tocilizumab antibodies was infrequent and did not appear to impact efficacy. Anti-tocilizumab antibodies were present in most patients with serious infusion reactions. Infusion reactions leading to withdrawal of tocilizumab treatment occurred in 0.3% of tocilizumab-treated patients.

The Phase 3 program has identified and characterized the safety risks that can be detected in a database of the size of tocilizumab's clinical development program. Long-term follow-up will be required to more closely investigate low incidence events. Roche proposes to add a tocilizumab cohort to an existing US registry and three European registries to acquire additional general long-term safety data and to further assess malignancy, cardiovascular effects, and GI perforations.

The overall benefit/risk profile for tocilizumab in patients with RA is favorable. Tocilizumab provides a new therapeutic option for patients with moderately to severely active RA who are naïve to DMARD treatment or who have had an inadequate response to one or more DMARDs or TNF antagonists.

## **2. BACKGROUND AND RATIONALE FOR THE DEVELOPMENT OF ACTEMRA (TOCILIZUMAB) IN THE TREATMENT OF RHEUMATOID ARTHRITIS**

This document provides background information on the clinical development program for Actemra and summarizes the efficacy and safety data supporting its use in the treatment of RA.

### **2.1 Current Treatment and Unmet Medical Need**

RA is a chronic, destructive inflammatory disease with both articular and systemic manifestations that affects approximately 0.5-1% of the population worldwide [1, 2, 3].

Early and aggressive treatment is important to control the long-term morbidity associated with the disease [4, 5, 6]. MTX, as well as other DMARDs, are front line therapies. In addition, advances in the molecular understanding of immunology and inflammation have led to the introduction of novel biologic therapies such as the TNF- $\alpha$  antagonists.

Despite these treatment advances, approximately 30-40% of patients with established RA fail to respond adequately to existing therapies and 50-60% of patients fail to achieve a major clinical response (by American College of Rheumatology [ACR] criteria) or good EULAR response [7]. Even among responders, the majority do not achieve remission [7]. Additionally, many patients experience toxicity or lose their response within 2-3 years of starting treatment [8 to 13].

Thus, there is a need for additional unique and mechanistically specific therapies to expand the availability of effective treatment options to ameliorate painful joint inflammation and prevent disability in RA patients.

### **2.2 Rationale for Anti-IL-6**

IL-6 is a multi-functional cytokine produced by a variety of cell types. It has been implicated in the pathogenesis of a variety of disease states including inflammatory diseases. Elevated serum IL-6 levels have been reported in RA patients compared with controls and in synovial fluid compared to serum, reflecting local production of IL-6 by the synovium [14, 15]. IL-6 levels correlate with disease activity in RA [14] and improvements associated with DMARD use are accompanied by a reduction in serum IL-6 levels [16]. Based on the potential role of IL-6 in the pathogenesis of RA, a humanized monoclonal antibody to IL-6R is expected to have efficacy in the treatment of RA.

#### **2.2.1 IL-6 Production and Distribution in Healthy Subjects**

IL-6 is a cytokine produced by multiple cell types, including lymphocytes, fibroblasts, synoviocytes, and endothelial cells and helps regulate hematopoiesis, stimulate inflammation, and mediate acute phase responses [17]. IL-6 is not constitutively expressed, but is induced by stimuli such as viral infections, lipopolysaccharide, IL-1 $\beta$ , and TNF- $\alpha$  [18].

IL-6 stimulates cells by two pathways: a classical signaling pathway and a unique trans-signaling pathway. In the classical pathway, IL-6 binds to mIL-6R and complexes

with gp130 to begin the signaling cascade. mIL-6R is present on hepatocytes, monocyte/macrophages, neutrophils, and leukocytes. In the trans-signaling process, IL-6 binds to sIL-6R that then binds to gp130 present on most cells [19]. The trans-signaling process enables cells that do not possess mIL-6R to respond to IL-6 signaling.

The pleiotropic nature of IL-6 suggests that changes in levels might result in various physiologic and adaptive changes and laboratory findings in vivo [20].

### **2.2.2 Association of Elevated IL-6 Levels and Inflammation**

IL-6 has been found in the synovial joints of patients with active RA and has been implicated in the pathogenesis of local joint damage and synovitis. Serum IL-6 and sIL-6R levels are also increased and the release of IL-6 or IL-6/sIL-6R complexes from the joint to the bloodstream contributes to the numerous systemic manifestations of the disease. Acutely, IL-6 stimulates hepatocytes to produce acute phase proteins such as CRP, fibrinogen,  $\alpha$ -1-antitrypsin, and serum amyloid A (SAA) [20]. IL-6 also induces the synthesis of the iron regulatory peptide, hepcidin, that may cause anemia by blocking GI iron absorption and utilization [21, 22]. In addition, IL-6 induces osteoclast differentiation, presumably contributing to joint destruction and osteoporosis [20].

### **2.3 Mechanism of Action – Changes in Inflammatory Cells and Mediators following Treatment with Tocilizumab**

Actemra (tocilizumab; also known as MRA) is a recombinant humanized mouse anti-human IL-6R monoclonal antibody that binds specifically to both sIL-6R and mIL-6R. Tocilizumab was created by grafting the complementary determining region of the mouse anti-human IL-6R monoclonal antibody onto a human IgG<sub>1</sub> $\kappa$  antibody framework. It is produced in Chinese hamster ovary cells by transfection of the genes for both the light and heavy chains into such cells.

This first in class drug has been shown to inhibit both sIL-6R- and mIL-6R-mediated signaling. Tocilizumab binds with a similar affinity to both sIL-6R and mIL-6R. Since the tocilizumab/IL-6R complex lacks the ability to bind gp130, it cannot transduce the IL-6 signal and thus, lacks biological activity.

### **2.4 Non-Clinical Pharmacology**

Tocilizumab specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R with similar affinity, which is expected since the binding regions of both receptors have an identical amino acid sequence. In vitro studies demonstrate that tocilizumab inhibits IL-6 binding to and displaces already bound IL-6 from sIL-6R and that tocilizumab has a strong anti-IL-6 effect in the targeted range of therapeutic plasma concentrations.

The cynomolgus monkey was chosen as the pharmacologically relevant species because tocilizumab cross-reacts with cynomolgus monkey IL-6R under in vitro and in vivo conditions. In a cynomolgus monkey model of collagen-induced arthritis, tocilizumab was shown to prevent both the local joint and the systemic inflammatory disease manifestations. Tocilizumab did not cause increases of serum liver enzymes or changes in serum lipids or bilirubin in these experiments. Animals that developed anti-tocilizumab antibodies, however, did not exhibit a sustained therapeutic response, presumably because of reduced exposure to tocilizumab via antibody-complexing and clearance.

IL-6R inhibition does not markedly interfere with immune functions. The in vivo immunomodulatory consequences of inhibition of IL-6R signaling were investigated in mice using the mouse specific IL-6R antibody, MR16-1. These studies demonstrate that IL-6 inhibition per se does not affect the primary antibody response to a T-cell dependent antigen. The delayed-type hypersensitivity reaction was reduced only when IL-6R signaling was blocked during the induction phase, not later. The data suggest tocilizumab may inhibit T-cell priming rather than T-cell differentiation. Therefore, tocilizumab should not affect the development of T-cell memory and T-helper cell activity.

## **2.5 Non-Clinical Pharmacokinetics and Metabolism**

Tocilizumab pharmacokinetics and metabolism are consistent with those of other IgGs, which are characterized by a slow plasma clearance and low penetration into tissues.

Single-dose studies in rats and monkeys show low clearance of tocilizumab with a long half-life and a low volume of distribution indicating low tissue transferability. Non-linear pharmacokinetics were observed in cynomolgus monkeys (as in humans), whereas linear pharmacokinetics were observed in rats. In repeat-dose studies with weekly dosing in monkeys, steady state was reached following the fifth or sixth administration.

Both the distribution and elimination of tocilizumab was as expected for an IgG antibody. Distribution studies showed no accumulation in any specific tissues, with the highest levels of radioactivity in monkeys observed in the adrenal gland, lung, kidney, liver, and the target tissues of tocilizumab, such as the synovia, membrana synovialis, bone marrow, and spleen. Tocilizumab is assumed to be catabolized by endogenous proteolytic pathways and the majority of radio-labeled tocilizumab is excreted in the urine as low-molecular-weight entities.

## **2.6 Toxicology and Safety Pharmacology**

Tocilizumab was well tolerated in cynomolgus monkeys, both as single intravenous (IV) doses up to 100 mg/kg and when given in multiple IV doses up to 50 mg/kg/day for 4 weeks or at IV doses up to 100 mg/kg/week for 6 months. No major abnormal findings were observed in either the clinical pathology investigations or in the histopathological evaluation of tissues. The systemic steady state exposure to tocilizumab in these studies was 8- to 10-fold above the maximum human exposure comparing trough levels in the animals with the maximum level measured in clinical trials. There were no treatment effects on serum lipid levels, serum transaminases, or on the morphology of the primary or secondary organs of the immune system.

A trend towards reduction of neutrophils was observed in the 2-week toxicity study (0.4, 2, 10, or 50 mg/kg tocilizumab daily) and a more pronounced reduction of neutrophils was observed in the 4-week daily treatment cynomolgus study (2, 10, or 50 mg/kg tocilizumab). The maximum reduction was 60% (compared with pre-treatment baseline) and was observed in the 50 mg/kg (high dose) group treated daily for 4 weeks. Effects on neutrophil counts were not seen in the single-dose nor in the 6-month repeat-dose toxicity study with one treatment per week. However, this lack of effect may be due to the fact that plasma concentrations of tocilizumab following weekly administration in this study were approximately 3-fold lower than observed in the 50 mg/kg group in the 1-month toxicity study in which animals were dosed daily. No

infections were observed in any affected animals. None of the monkeys (N=50) from the 4-week or the 6-month toxicity study developed an opportunistic infection.

Tocilizumab did not adversely affect cardiac integrity or electrophysiology; an alteration of blood pressure was not observed in any of the preclinical studies. These results suggest that tocilizumab did not alter the structure or function of the heart.

Standard genotoxicity studies with tocilizumab in both prokaryotic and eukaryotic cells were negative. A carcinogenicity study of tocilizumab has not been conducted. As tocilizumab does not bind to rodent IL-6R, conventional long-term cancer studies in rats or mice are inappropriate to assess a function-associated carcinogenic potential of tocilizumab. Furthermore, IgG1 monoclonal antibodies are not deemed to have an intrinsic carcinogenic potential.

An embryo-fetal toxicity study of tocilizumab conducted in cynomolgus monkeys showed no evidence of a teratogenic potential. A slight increase of abortion/embryo-fetal death was observed with high systemic exposure in the 50 mg/kg/day (highest dose) group compared with placebo and lower dose groups. Because IL-6 has no known regulatory role in normal fetal development or immunological control of pregnancy, the relevance for human pregnancy is unknown.

Multiple dose studies in cynomolgus monkeys, in which the active compound was given IV in high dose volumes, showed that tocilizumab was well tolerated locally. Additional local IV, subcutaneous, or intramuscular tolerance studies in rabbits also showed excellent local tolerability of tocilizumab and its formulation ingredients.

### **3. REGULATORY HISTORY**

Roche has had ongoing interactions with the Food and Drug Administration (FDA) during the development of tocilizumab on the design and analysis plans for the Phase 3 studies and on the adequacy of the collected data to support submission of a Biologic License Application (BLA) for review (pre-IND/pre-Phase 3 meeting, pre-BLA feedback).

Roche filed a complete BLA with FDA in November, 2007 for the following indication:

*Actemra<sup>®</sup> (tocilizumab) is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who are naive to treatment with, or who had an inadequate response to, one or more DMARDs or TNF antagonists. Actemra can be used alone or in combination with methotrexate or other DMARDs.*

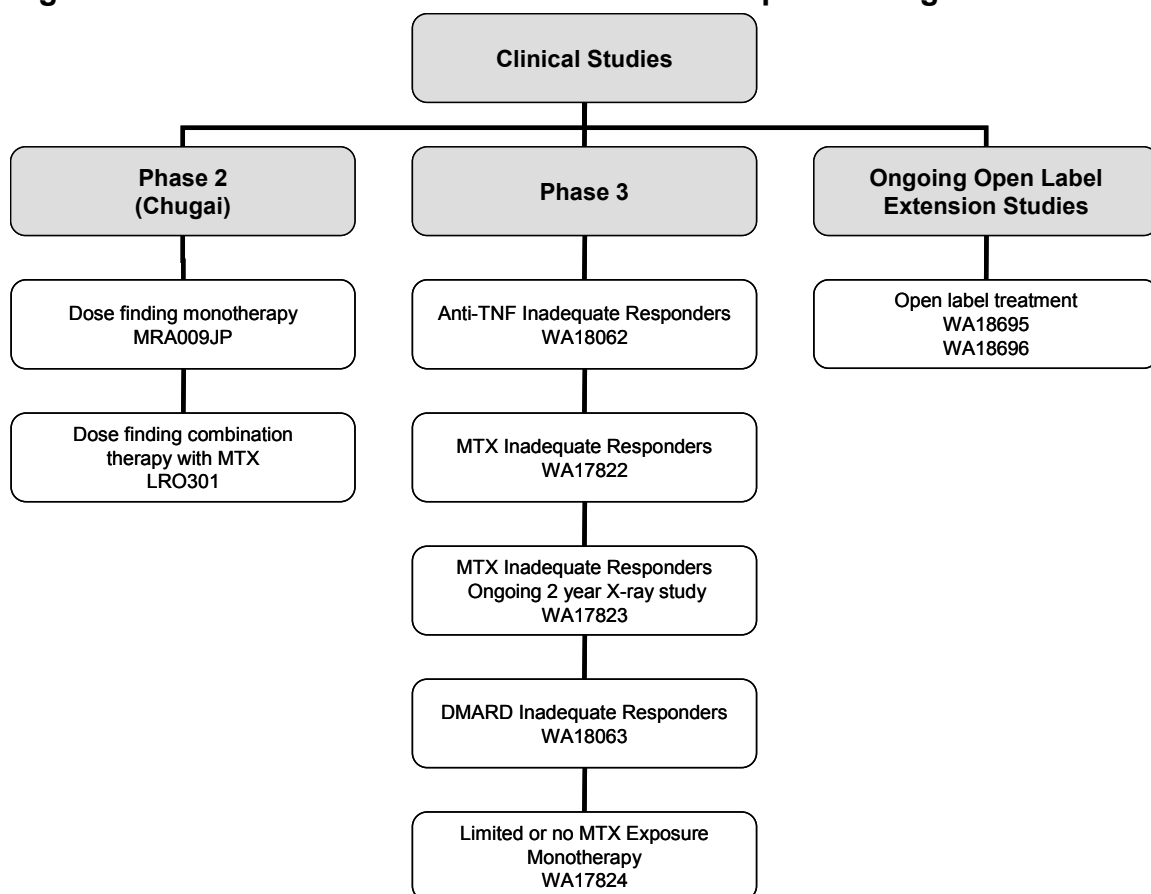
Longer-term (1 and 2 year) efficacy and safety data to support expansion of the indication to include additional efficacy claims for inhibition of progression of structural damage, inducing major clinical response, and improvement of physical function will be provided in subsequent supplemental filings. In addition, Roche has had interactions with the Agency regarding a pediatric development program in both systemic juvenile idiopathic arthritis (sJIA) and polyarticular-course juvenile idiopathic arthritis (pJIA). These development programs have recently been initiated.

#### 4. OUTLINE OF DEVELOPMENT PROGRAM

Roche's co-development partner, Chugai Pharmaceuticals, completed a development program for tocilizumab and obtained approval in Japan for the treatment of Castleman's disease in 2005. In April 2008, tocilizumab was also approved in Japan for the treatment of adult RA (for reducing signs and symptoms and inhibiting the progression of structural joint damage), sJIA, and pJIA. Chugai conducted an extensive Phase 1 program in the UK and Japan, Phase 2 efficacy and safety studies in Europe and Japan, and Phase 3 studies in Japan. These studies were provided as supportive data in the BLA and the Four Month Safety Update (4MSU) submitted to FDA. Patients in the Chugai program have been followed for up to 5 years.

The Roche clinical development program was designed to assess the safety and efficacy of tocilizumab in the treatment of signs and symptoms of moderately to severely active RA in a broad patient population and included patients who were naïve to treatment with traditional DMARDs as well as patients who had an inadequate response to existing therapeutic agents including non-biologic DMARDs and TNF-antagonist therapies. The program consisted of two dose-finding, Phase 2 studies that were part of the original Chugai development program and five pivotal multicenter, randomized, double-blind, controlled, Phase 3 trials and two open-label, long-term treatment extensions that were conducted by Roche (Figure 1).

**Figure 1 Overview of Roche Clinical Development Program**



As previously mentioned, both of the Phase 2 dose finding studies were conducted by Chugai. One was a 12-week, double-blind, placebo-controlled, randomized study conducted in Japan with tocilizumab given as monotherapy (study MRA009JP). The second was a 20-week, double-blind, parallel-group, placebo-controlled, randomized, seven-arm, dose-finding study conducted in Europe with 2, 4, or 8 mg/kg of tocilizumab given alone or in combination with MTX (study LRO301). Based on the positive outcome of these Phase 2 studies, doses of tocilizumab 4 and 8 mg/kg were explored in Roche's Phase 3 studies.

The multicenter, double-blind, placebo-controlled Phase 3 trials included four 24-week studies designed to assess a reduction in signs and symptoms of RA and one interim analysis of 24-week data from an ongoing 2-year study designed to evaluate physical function and prevention of joint damage. These studies investigated the use of tocilizumab as monotherapy or in combination with MTX and/or other commonly prescribed DMARDs in adult patients (18 years and older) with moderately to severely active RA.

In addition, the development program includes two long-term, open-label, extension studies into which patients who completed the 24-week, pivotal Phase 3 studies were eligible for enrollment. Patients in these studies are receiving tocilizumab 8mg/kg, mostly in combination with MTX or other DMARDs. These studies were designed to provide long-term safety information and data regarding tocilizumab's durability of efficacy.

An overview of the key design features of the Phase 3 clinical program is provided in [Table 3](#). All five pivotal Phase 3 studies included ACR20 response as a primary endpoint. All five studies also included provisions for the adjustment of study medication for patients with an inadequate response, referred to as escape therapy. The two open-label extension studies are similar in design and, therefore, data from these studies are presented together. Additional information on study design, endpoints, and the presentation of efficacy and safety data is provided in [Sections 6 and 7](#).

**Table 3 Key Design Features of the Pivotal Phase 3 Studies**

Study/No. of Patients	WA17822 N = 623	WA17823 N = 1196	WA17824 N = 673	WA18062 N = 499	WA18063 N = 1220	WA18695 N = 537**	WA18696 N = 2025**
<b>Patient Population</b>	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
<b>Primary Endpoint at Week 24</b>	ACR20	ACR20	ACR20	ACR20	ACR20	Long-term safety/efficacy	Long-term safety/efficacy
<b>Design and Duration</b>	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*
<b>Treatment</b>	<b>3 arm study:</b> tocilizumab: 4 or 8 mg/kg or placebo IV every 4 weeks + MTX 10-25 mg/week	<b>3 arm study:</b> tocilizumab: 4 or 8 mg/kg or placebo IV every 4 weeks + MTX 10-25 mg/week	<b>2 arm study:</b> tocilizumab: 8 mg/kg iv every 4 weeks <b>or</b> MTX 7.5-20 mg/week (po) <b>Substudy includes 3<sup>rd</sup> arm:</b> Placebo (8 weeks placebo then 16 weeks TCZ 8 mg/kg)	<b>3 arms:</b> tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks plus MTX 10-25 mg/week	<b>2 arms:</b> tocilizumab: 8 mg/kg or placebo IV every 4 weeks plus standard DMARD(s)	<b>1 arm:</b> tocilizumab: 8 mg/kg IV every 4 weeks plus MTX	<b>1 arm:</b> tocilizumab: 8 mg/kg IV every 4 weeks alone or plus MTX / other DMARD(s)
<b>Escape therapy</b>	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	-	-

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



## 5. CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics of Tocilizumab

The pharmacokinetic information on tocilizumab was obtained from the population pharmacokinetic analysis of four Phase 3 studies in 1793 RA patients with supportive data from non-compartmental analyses of clinical pharmacology studies.

The total clearance of tocilizumab is concentration dependent and is the sum of the non-linear and linear clearances. The concentration-dependent, non-linear clearance plays a major role at low tocilizumab concentrations via binding to IL-6R. Once this non-linear clearance pathway is saturated at higher tocilizumab concentrations, clearance is mainly linear and mediated by the reticuloendothelial system. The latter represents the same route of elimination as for all other IgG antibodies [23, 24]. As a consequence of the non-linear clearance, the pharmacokinetic characteristics of tocilizumab are concentration- and dose-dependent at low exposures.

The volume of distribution of the central compartment of tocilizumab was 3.5 L, which is in the range of what has been previously described for IgGs and other monoclonal antibodies. The volume of distribution at steady-state ( $V_{ss}$ ) (6.4 L) tends to indicate a limited distribution into the body. However, for most antibodies, distribution into tissues is often part of the elimination process and not part of the distribution process and hence contributes to their small apparent distribution volumes. Thus, a small  $V_{ss}$  should not necessarily be interpreted as low tissue penetration and adequate concentrations may be reached in a single target organ.

The pharmacokinetic parameters of tocilizumab are provided in Table 4. These parameters did not change with time. A more than dose proportional increase in area under the concentration-time curve (AUC) and trough concentration ( $C_{min}$ ) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration ( $C_{max}$ ) increased dose-proportionally. At steady-state, predicted AUC and  $C_{min}$  were higher at 8 mg/kg as compared with 4 mg/kg. For the 4 mg/kg and 8 mg/kg doses, steady-state was achieved for  $C_{max}$ , AUC, and  $C_{min}$  following the first administration, after 8 weeks, and after 20 weeks, respectively.

The  $t_{1/2}$  of tocilizumab is concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective  $t_{1/2}$  decreased with decreasing concentrations within a dosing interval from 14 days to 8 days.

**Table 4** Simulated Mean (SD) AUC,  $C_{max}$  and  $C_{min}$  after 48 Weeks of Treatment with Tocilizumab 4 and 8 mg/kg every 4 weeks

	AUC <sub>τ</sub> (μg*h/mL)	C <sub>max</sub> (μg/mL)	C <sub>min</sub> (μg/mL)
4 mg/kg q4wks	13000 (5800)	88.3 (41.4)	1.49 (2.13)
8 mg/kg q4wks	35000 (15500)	183.4 (85.6)	9.74 (10.5)

Age, gender, race, and ethnicity had no impact on the pharmacokinetics of tocilizumab. Body size (body surface area, body weight, body mass index) affected linear clearance

(CL) in a similar manner in that an increase in body size resulted in an increase in linear CL. This was accounted for by body weight-adjusted dosing, although this adjustment results in slightly higher exposures to tocilizumab with higher body weight.

Tocilizumab is not metabolized via the CYP450 or the P-glycoprotein pathway. Therefore, a direct interaction with substrates, inhibitors or inducers of CYP450 and/or P-glycoprotein with the pharmacokinetics of tocilizumab is not expected and no formal studies have been performed. Population pharmacokinetic analysis from the Phase 3 trials revealed that use of concomitant medications for RA did not influence the pharmacokinetics of tocilizumab.

A recognized effect of inflammation is suppression of CYP450 enzyme levels. A reduction of inflammation following treatment with tocilizumab may normalize CYP450 levels. Data from a study in RA patients [study MRA220JP] indicated that the systemic exposure of concomitantly administered CYP450 substrates can decrease with the inhibition of IL-6 signaling to exposures observed in patients without inflammatory disease.

Drug-drug interaction studies have been conducted with tocilizumab in patients with RA. These studies used drugs that were metabolized by CYP3A4 (simvastatin), CYP2D6 (dextromethorphan) and CYP2C19 (omeprazole). Note that the simvastatin data have only recently become available and have not been submitted to nor reviewed by FDA. These data are provided in a supplemental report (Section 12) .

Simvastatin levels were taken prior to administration of tocilizumab and were elevated as compared to values reported in the literature, consistent with the known effect of IL-6 on CYP450 suppression. A decrease of 57% of simvastatin exposure 1 week after administration of tocilizumab was found. For dextromethorphan, no changes in exposure were noted and for omeprazole, a 50% reduction was found in CYP2C9 extensive metabolizers. In-vitro data and in-vivo data with IL-6 suggests that for other CYP450s, the effect will be less than that of CYP3A4.

Taken together, these data are clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. Upon initiation of tocilizumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (eg, warfarin) or drug concentration (eg, cyclosporine) should be performed and the individual dose of the medicinal product adjusted as needed.

## **5.2 Pharmacodynamics**

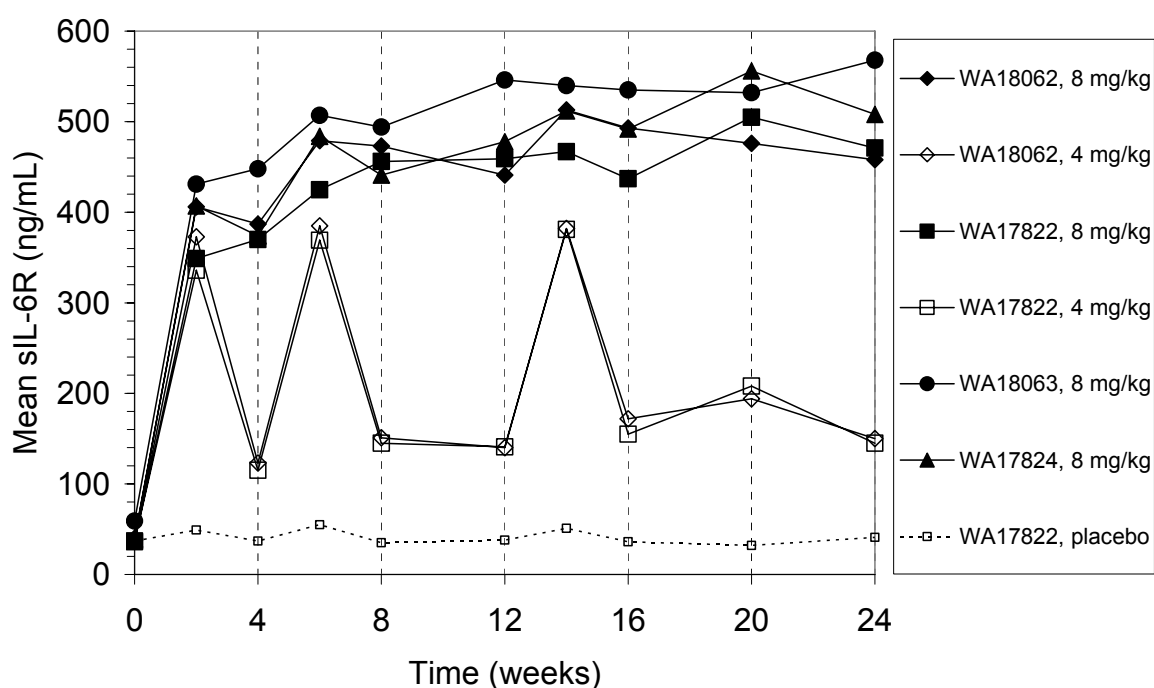
### **5.2.1 sIL-6**

For both tocilizumab doses, mean sIL-6R trough levels increased with increasing treatment duration until approximately weeks 8 to 12 (Figure 2). For the 4 mg/kg dose, trough sIL-6R levels increased slightly with treatment duration. Highest mean sIL-6 levels for tocilizumab 4 mg/kg were 5.1- to 5.6-fold above baseline. Peak sIL-6R levels were achieved at weeks 2, 6, and 14 (ie, in the middle of the dosing interval). For the 8 mg/kg dose, mean sIL-6R levels remained high and increased with treatment duration with minor fluctuations within the dosing interval. Highest mean sIL-6R levels for

tocilizumab 8 mg/kg were 10- to 14-fold above baseline. For each dose, there were no clear differences across studies taking into account the variability observed.

The sustained increase in sIL-6R levels observed for the 8 mg/kg dose suggests persistent binding of tocilizumab to sIL-6R. At the 4 mg/kg dose, the fluctuating levels of sIL-6R suggest that tocilizumab exposure is below that for consistent binding of tocilizumab to sIL-6R.

**Figure 2**      **Mean sIL-6R Levels in Patients Treated with 4 and 8 mg/kg Tocilizumab every 4 Weeks in Four Phase III Studies (WA17822, WA17824, WA18062 and WA18063)**



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

### 5.2.2 IL-6

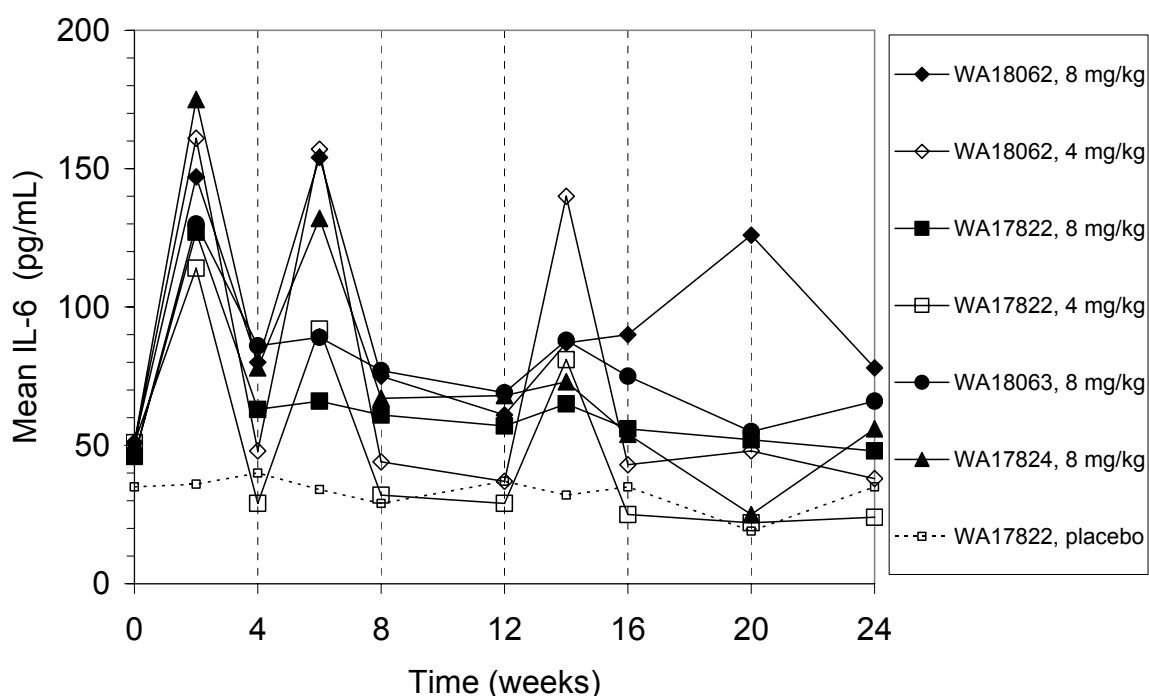
For the tocilizumab 4 and 8 mg/kg doses, mean IL-6 levels peaked at week 2 (ie, following the first administration of tocilizumab), with a general decrease in peak levels over time (Figure 3). Across the studies, lower mean trough IL-6 levels were observed for the 4 mg/kg dose compared with the 8 mg/kg dose.

For the 4 mg/kg dose (studies WA17822 and WA18062), mean IL-6 levels peaked at weeks 2, 6, and 14 (ie, at all occasions where IL-6 levels were assessed 2 weeks post-dose). Peak levels were of similar magnitude in both studies, with slightly lower values with increasing treatment duration in study WA17822. Mean trough IL-6 levels were similar to baseline values for this dose.

For the 8 mg/kg dose, a lower peak or no peak was observed at weeks 6 and 14, except for study WA18062, where the second peak was similar to the first peak. In this study, IL-6 levels increased towards the end of the treatment period. It is of note that the peak at week 20 is driven by outliers as this was not observed for median values. Mean trough IL-6 levels were generally higher than baseline values for this dose.

Taken together, these data show that IL-6 temporarily increases following administration of tocilizumab. This increase is most likely caused by blockade and displacement of its receptor by tocilizumab. Subsequently, there was a trend for decreasing IL-6 peak levels over 24 weeks for tocilizumab 8 mg/kg suggesting an adaptation of IL-6 regulation with amelioration of the disease or inflammatory status.

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



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

### 5.2.3 CRP

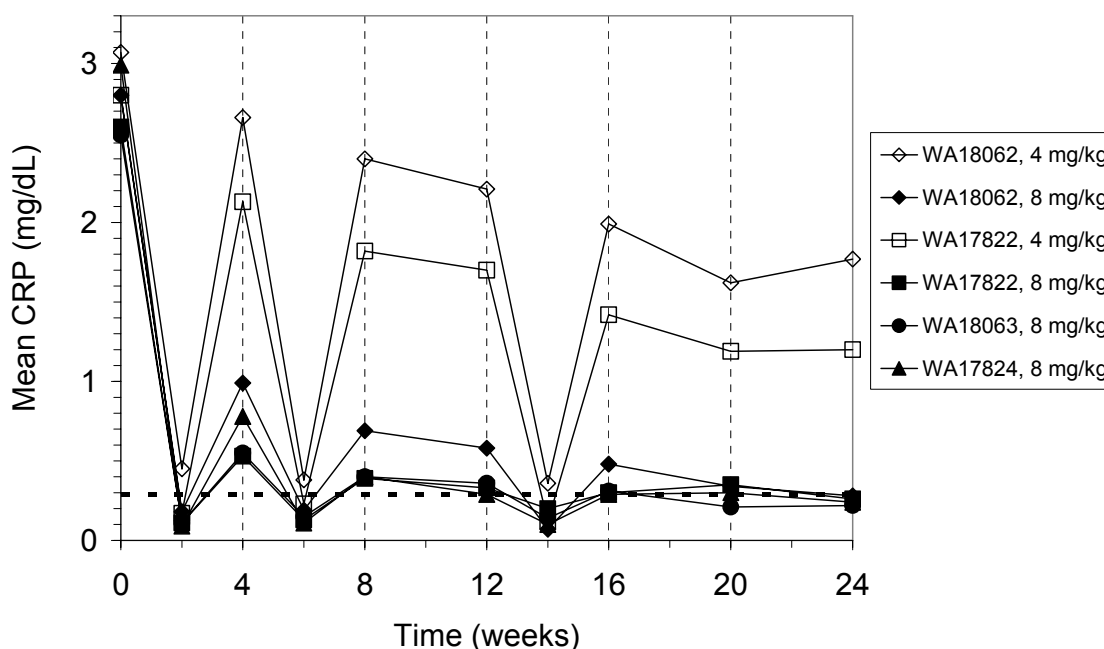
CRP is synthesized by hepatocytes as a direct effect of IL-6 stimulation. Elevated CRP levels are an indication of the intensity of inflammation in RA. Through its blockade of IL-6R, tocilizumab is expected to lower CRP.

For the 4 mg/kg dose, a moderate decrease in mean CRP trough levels was observed up to week 24 (Figure 4). Mean trough levels ranged from 1.62 to 2.66 mg/dL (baseline 3.07 mg/dL) and from 1.19 to 2.13 mg/dL (baseline 2.8 mg/dL) for WA18062

and WA17822, respectively. Levels fluctuated within the dosing interval with considerably lower levels 2 weeks post-dose (weeks 2, 6 and 14), ranging from 0.36 to 0.45 mg/dL and from 0.12 to 0.23 mg/dL in studies WA18062 and WA17822, respectively.

For the 8 mg/kg dose, a pronounced and sustained decrease in mean CRP trough levels was observed. Mean CRP levels at week 4 ranged from 0.53 to 0.99 mg/dL with mean baseline levels ranging from 2.55 to 2.99 mg/dL. Mean trough levels decreased with time and ranged from 0.22 to 0.28 mg/dL at week 24. Furthermore, mean levels at 2 weeks post-dose were similar for patients treated with 4 and 8 mg/kg. For 8 mg/kg, mean CRP levels 2 weeks post-dose ranged from 0.07 to 0.20 mg/dL.

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



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

## 5.3 Pharmacokinetic/Pharmacodynamic Relationships

### 5.3.1 Efficacy

There was a clear relationship between tocilizumab systemic exposure and ACR response, DAS28, and markers of inflammation such as CRP with response improving with increasing exposure. DAS28 was selected as the dependent variable for the population pharmacokinetic/pharmacodynamic analysis of tocilizumab. An indirect response model was applied to characterize the link between tocilizumab serum concentration and DAS28. The main pharmacokinetic parameters were  $EC_{50}$  (the tocilizumab concentration at which 50% of the maximum tocilizumab effect is reached) and  $E_{max}$  (the maximum effect of tocilizumab on DAS28 ‘production rate’).  $EC_{50}$  was estimated at 3.72  $\mu\text{g/mL}$ .

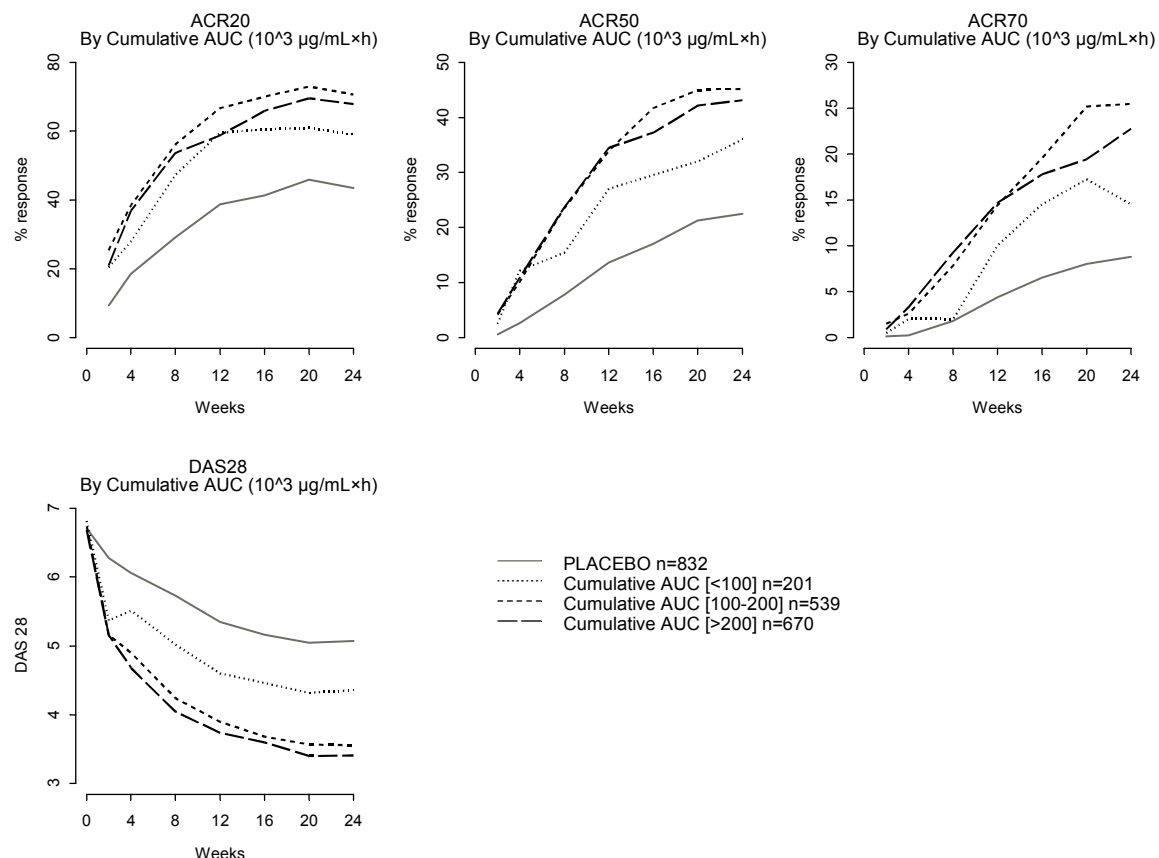
and  $E_{\max}$  was estimated at 72.5%. This means that a DAS28 of 6.8 at baseline would be reduced to 1.2.

At a dose of 8 mg/kg every 4 weeks, 95% of patients had tocilizumab concentrations above the  $EC_{50}$  after 2.5 weeks with 50% of the patients still above  $EC_{50}$  prior to the next infusion. At a dose of 4 mg/kg every 4 weeks, 50% of patients had tocilizumab concentrations above the  $EC_{50}$  after 2.5 weeks, with only about 5% of the patients still above  $EC_{50}$  prior to the next infusion.

For the two clinical endpoints, ACR and DAS28, an exposure-response relationship was observed (Figure 5). The ACR20, ACR50, and ACR70 response rates increased with time for all three exposure categories ( $AUC < 100 \times 10^3 \mu\text{g}\cdot\text{h/mL}$  [low];  $100\text{--}200 \times 10^3 \mu\text{g}\cdot\text{h/mL}$  [medium], and  $> 200 \times 10^3 \mu\text{g}\cdot\text{h/mL}$  [high]). Patients in the medium and high exposure categories showed the highest increases in response rates, but the response rates in these two categories overlapped. Patients in the low exposure category showed a lower response rate than those in the medium and high categories, but a higher response rate than placebo-treated patients. These results show that patients dosed with 8 mg/kg had higher response rates than those dosed with 4 mg/kg.

An exposure-dependent decrease was observed for DAS28 (Figure 5). The decline in DAS28 with time was of a similar magnitude in patients in the medium and high exposure categories, but a consistently lower DAS28 was observed for patients in the high exposure category.

**Figure 5 Effect of Tocilizumab Exposure on ACR20, ACR50, ACR70 Response Rates and DAS28 (WA17822, WA17824, WA18062 and WA18063)**



Top row: lines represent the percentage of patients with positive ACR response  
Bottom row: lines represent the mean DAS28 response

### 5.3.2 Safety

Graphical analysis of the relationship between tocilizumab exposure and the main safety parameters indicated that high exposures were not associated with a higher occurrence of adverse events or serious adverse events.

Slight increases in total bilirubin, ALT, AST, total cholesterol, LDL cholesterol, and triglycerides were observed with increasing exposure to tocilizumab; the relationship was not strong and the data showed a high level of variability. For most of these parameters, compared to the lower exposure category, no further increases were observed at the two highest exposure categories, indicating a plateau effect had been reached at these exposure levels. There was no apparent effect of tocilizumab exposure on HDL cholesterol.

A clear exposure-response relationship was observed for white blood cells, hemoglobin, platelets, and neutrophils. Neutrophil count decreased with increasing exposure. Based on this relationship and the known pharmacodynamic effect of tocilizumab on neutrophils through blockade of IL-6 signaling, this parameter was selected for

pharmacokinetic/pharmacodynamic modeling. An indirect response model was used to describe the relationship between the time course of neutrophil count post-dosing and tocilizumab serum concentrations. The typical serum tocilizumab concentration at which 50% of the maximum tocilizumab effect ( $EC_{50}$ ) is reached was estimated at 7.42  $\mu\text{g/mL}$ . The maximum effect of tocilizumab on the stimulation of neutrophil loss from the blood compartment ( $E_{\text{max}}$ ) was estimated at 0.792, translating into a mean maximum decrease of circulating neutrophils of 44%.

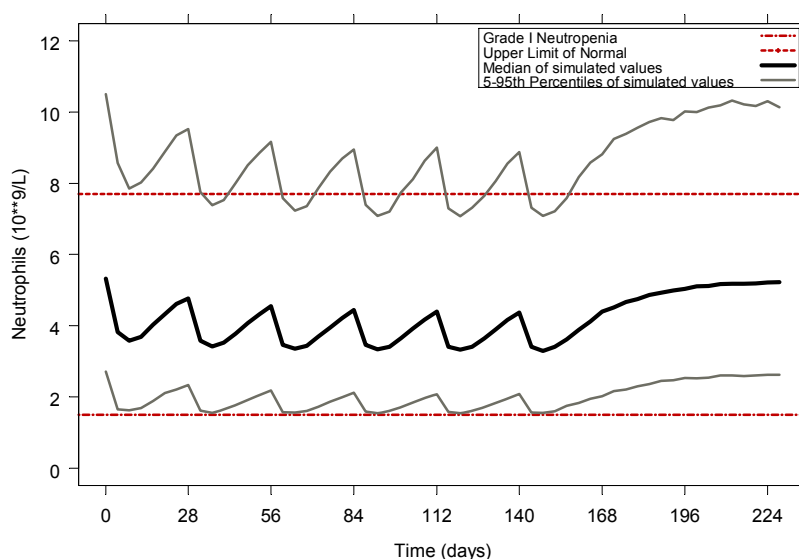
Simulations showed that the increased exposure with 8 mg/kg did not result in an increased incidence of Grade 4 neutropenia ( $< 0.5 \times 10^9/\text{L}$ ) (Table 5). For 8 mg/kg, fluctuations in neutrophil count between infusions were less pronounced than with 4 mg/kg (Figure 6 and Figure 7).

**Table 5 Simulated Percentage of Patients\* with NCI-CTC Grades 1 to 4 of Neutropenia for 4 and 8 mg/kg Tocilizumab**

	4 mg/kg				8 mg/kg			
	Mean	SD	Min	Max	Mean	SD	Min	Max
<b>Grade 1</b> ( $< \text{LLN}$ and $> 1.5 \times 10^9/\text{L}$ )	21.9	0.67	20.3	23.5	25.3	0.45	24.2	26.4
<b>Grade 2</b> ( $< 1.5$ and $> 1 \times 10^9/\text{L}$ )	13.5	0.69	11.7	15.4	16.7	0.50	15.1	17.8
<b>Grade 3</b> ( $< 1$ and $> 0.5 \times 10^9/\text{L}$ )	2.5	0.35	1.7	3.3	3.6	0.36	2.7	4.5
<b>Grade 4</b> ( $< 0.5 \times 10^9/\text{L}$ )	0.027	0.042	0.00	0.17	0.049	0.046	0.00	0.20

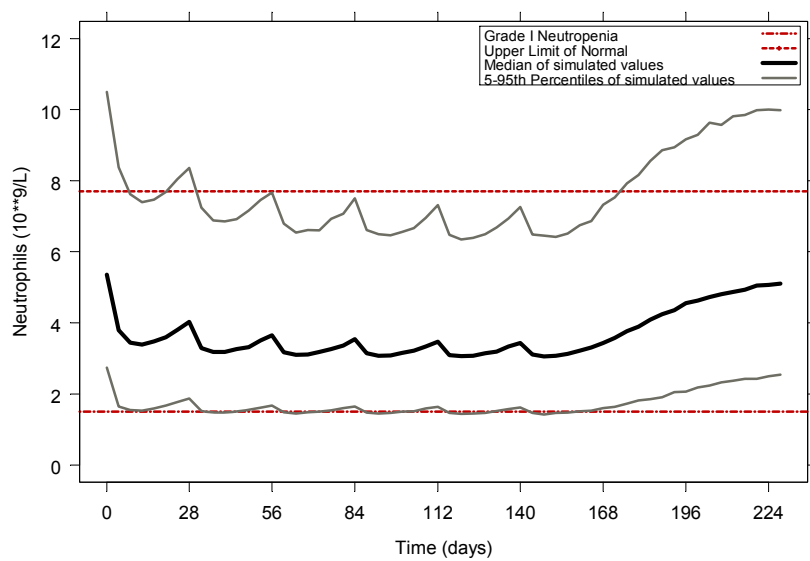
\*N = 108500; LLN lower limit of normal.

**Figure 6 Predicted Median Time Course of Neutrophils and 90% Prediction Interval at 4 mg/kg Tocilizumab every 4 Weeks**





**Figure 7**      **Predicted Median Time Course of Neutrophils and 90% Prediction Interval at 8 mg/kg Tocilizumab every 4 Weeks**



## **6. SUMMARY OF CLINICAL EFFICACY**

Given the strong association between IL-6 levels and RA symptoms, tocilizumab's ability to block conventional IL-6 signaling and trans-signaling provides a therapeutic option for the treatment of RA.

In all of the pivotal Phase 3 studies, the primary endpoint of ACR20 was met. In addition, treatment with tocilizumab resulted in significant improvements compared to control in the majority of secondary endpoints ([Appendix 2](#)).

The efficacy data demonstrate that:

- Tocilizumab is effective across a wide range of RA patients including:
  - DMARD-inadequate responders,
  - Anti-TNF-inadequate responders, and
  - Patients naïve to MTX/DMARDs
    - Tocilizumab monotherapy was superior to MTX monotherapy
- Tocilizumab alleviates the signs and symptoms of RA by
  - Consistent and robust effects on numerous endpoints particularly the more clinically relevant endpoints of ACR50, ACR70, and DAS28 < 2.6.
  - Rapid response within 2 weeks with continued improvement up to 2 years
  - Improvement in patients' quality of life
- 8 mg/kg of tocilizumab every 4 weeks was consistently more effective than 4 mg/kg in managing disease activity.

### **6.1 Introduction**

This section provides a summary of the data demonstrating the efficacy of tocilizumab when used alone or in combination with MTX or other DMARDs for reducing signs and symptoms in adult patients with moderately to severely active RA. The data presented are derived from five Phase 3, multicenter, randomized, double-blind, placebo-controlled studies and two ongoing, open-label, extension studies.

The Phase 3 program was extensive and enrolled 4211 patients ([Table 3](#)). Of these, 3810 patients (90%) completed 24 weeks of treatment (77% on initial therapy and 13% after entering escape therapy). Only patients who completed the four 24-week studies (WA17822, WA17824, WA18062, and WA18063) and not the ongoing 2-year study (WA17823), were eligible to enter the open-label extension studies. A total of 2715 of 3015 patients (90%) from the four double-blind, 24-week studies completed 24 weeks of treatment and were eligible to enter the open-label extension studies (2398 [80%] on initial therapy and 317 [10%] after entering escape therapy). Ninety-four percent of these patients elected to receive open-label treatment with 8 mg/kg of tocilizumab.

### **6.2 Selection of Dose for Phase 3 Studies**

Data from the Phase 2 clinical study conducted in Europe (study LR0301) were used to select the doses for the Phase 3 studies. This was a multicenter, double-blind, randomized, parallel group, controlled study where patients were allocated to one of seven treatment groups: tocilizumab 2, 4, or 8 mg/kg as monotherapy or in combination

with MTX, and a placebo group. The primary efficacy endpoint was the proportion of patients who achieved an ACR20 response at week 16.

The highest response rates were observed with tocilizumab 4 mg/kg and 8 mg/kg given as combination or 8 mg/kg given as monotherapy, particularly at the more clinically relevant endpoints of ACR50 and ACR70 ([Appendix 1](#)).

### 6.3 Efficacy Endpoints

The efficacy of tocilizumab was evaluated using validated measures as per FDA (February 1999) and EMEA (December 2003) guidances for industry on clinical development programs for products for the treatment of RA.

The ACR20 response at week 24 was the primary endpoint in all five double-blind studies. The ongoing pivotal study, WA17823, will also evaluate the efficacy of tocilizumab in inhibiting progression of structural damage with radiographs scored using the Genant modification of the Sharp scoring system (radiographic) and physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) as co-primary endpoints at weeks 52 and 104.

Secondary efficacy endpoints for all double-blind studies included clinically meaningful measures of disease activity and patient reported outcomes ([Table 6](#)). Assessment of disease activity included the more stringent ACR response criteria, ACR50 and ACR70, and ACR core set parameters as secondary endpoints. The EULAR measures of disease activity, including DAS28 were also secondary endpoints because DAS28 provides an assessment of disease activity at a point in time rather than a change from baseline as indicated by ACR responses. Patient-reported outcomes also included evaluations of fatigue and general mental and physical health assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) and the short-form health survey (SF-36), both validated in RA patients [[25](#), [26](#), [27](#)].

Maintenance of effect (up to 2 years of open-label therapy following 6 months of double-blind therapy) was also assessed (ACR, DAS28, and EULAR responses).

A summary of the primary and secondary efficacy endpoints for the five pivotal studies is provided in [Table 6](#).

**Table 6 Phase 3 Studies: Primary and Secondary Endpoints**

<b>Primary</b>	<ul style="list-style-type: none"> <li>Proportion of patients with ACR20 responses at 24 weeks</li> </ul>
<b>Secondary</b>	<ul style="list-style-type: none"> <li>Proportion of patients with ACR50 and ACR70 responses at 24 weeks</li> <li>Mean changes from baseline in the individual parameters of ACR core set at 24 weeks</li> <li>Change in DAS28 from baseline at 24 weeks</li> <li>Proportion of patients with DAS28 score &lt;2.6 at 24 weeks</li> <li>Proportion of patients classified as categorical DAS28 responders (EULAR response) at 24 weeks</li> <li>Mean changes from baseline in SF-36 and FACIT fatigue scale scores at 24 weeks</li> </ul>

## **6.4 Analytical Methods and Data Presentation**

Efficacy data were analyzed for an intent-to-treat (ITT) and per protocol (PP) population. The ITT population, defined as all randomized patients who received at least one administration of study medication, was the primary analysis population for all of the Phase 3 studies except the monotherapy trial (WA17824) which used the PP population, as the study was intended to demonstrate non-inferiority.

For the four combination therapy studies (WA17822, WA17823, WA18062, and WA18063), a two-sided 5% significance level was used to determine superiority of tocilizumab compared with placebo. The primary analysis was the Cochran-Mantel-Haenszel chi-squared test with adjustment for the stratification factor applied at randomization. In the monotherapy study, WA17824, the statistical hypotheses were based on a non-inferiority comparison of the tocilizumab 8 mg/kg group against MTX using the extended Mantel-Haenszel statistic. Non-inferiority was determined if the lower limit of the 95% confidence interval (CI) for the treatment difference between tocilizumab and placebo was  $\geq -0.12$ . If the lower limit of the 95% CI for the treatment difference was  $> 0$ , then the corresponding p-value for superiority was also produced for the comparison of ACR20, ACR50, and ACR70.

A primary method for handling missing data was predefined for all endpoints. In addition, all primary methods were subjected to sensitivity analyses in which other methods were explored.

To control the rate of false positive conclusions due to the number of secondary endpoints, a prospectively defined fixed sequence approach was applied to statistical testing for each individual study and any pooled analysis. This approach allowed the testing of each of the null hypotheses for each secondary endpoint at the same significance level of  $\alpha$  (5%) without any adjustment, as long as the null hypotheses were tested in a predefined hierarchical order. For the primary analyses, patients who received escape therapy, discontinued for any reason, or did not have sufficient data to calculate an ACR response were considered non-responders.

### **6.4.1 Data Presentation and Pooling Strategy**

Efficacy data are presented for: 1) patients treated in the double-blind controlled studies, and 2) patients who entered and received at least one dose of tocilizumab in the open-label extension studies.

#### **6.4.1.1 Double-blind Controlled Studies**

Data from studies WA17822, WA17823 (interim analysis of 24-week data), and WA18063 (DMARD-inadequate responder population) were pooled as these three studies were similar in design, included similar patient populations and outcome measures, utilized the same data collection instruments, and all three studies met the primary endpoint and key secondary endpoints. Efficacy data are presented for three groups: tocilizumab 4 mg/kg + MTX group, tocilizumab 8 mg/kg + DMARD group, and placebo + DMARD group.

Efficacy data from study WA17824 (monotherapy) and study WA18062 (anti-TNF-inadequate responder population), conducted in different patient populations, are presented separately.

#### **6.4.1.2 Long-term Efficacy**

For the assessment of long-term efficacy, data from the double-blind, controlled studies and the open-label extension studies were combined to give a long-term overview of efficacy in patients treated with tocilizumab. To allow within-patient comparisons of efficacy from the double-blind controlled studies into the open-label extension studies, data are presented by the original treatment group and original baseline in the double-blind controlled studies.

### **6.5 Efficacy in Combination Therapy**

#### **6.5.1 Patients with an Inadequate Response to DMARDs**

Studies WA17822, WA17823, and WA18063 included patients who had previously experienced an inadequate clinical response to treatment with MTX and/or other traditional DMARDs.

In studies WA17822 and WA17823, all patients had to have received MTX for  $\geq 12$  weeks before randomization, with at least 8 weeks prior to baseline being at a stable dose of between 10 to 25 mg/week. Patients were randomized (1:1:1) to either tocilizumab doses of 8 mg/kg or 4 mg/kg given in combination with MTX or to MTX/placebo ([Table 7](#)).

In study WA18063, patients had to have been on stable doses of permitted DMARDs for at least 8 weeks prior to baseline. In study WA18063, patients were randomized in a 2:1 ratio to tocilizumab 8 mg/kg + DMARDs or DMARDs/placebo.

In all three of these studies, stable doses of oral corticosteroids ( $\leq 10$  mg/day prednisone or equivalent) and NSAIDs were also permitted during the 24-week treatment period.

Patients who completed 24 weeks of therapy in studies WA17822 and WA18063 were eligible to enter the long-term extension studies, where all patients received treatment with tocilizumab at a dose of 8 mg/kg.

Study WA17823 is an ongoing, 2-year study designed to evaluate physical function and prevention of joint damage. This study has its own open-label extension period. Signs and symptoms data from the interim analysis at 24 weeks is provided in the following sections. One year data, including radiographic data, from the second interim analysis are presented in a supplemental report (Section [13](#)). These data have recently become available and have not been submitted to nor reviewed by the FDA.

**Table 7                      Design of Studies including DMARD-Inadequate Responders**

	DMARD-Inadequate Responders		
	WA17822	WA17823	WA18063
Background medication	MTX	MTX	DMARDs*
Tocilizumab doses	4, 8 mg/kg	4, 8 mg/kg	8 mg/kg
Control	Placebo	Placebo	Placebo
Primary Endpoint	24 week	Interim analysis at 24 weeks**	24 weeks
ACR20			
Patient population	MTX IR	MTX IR	DMARD IR
Extension period	Open-label study WA18695	Open-label for 3 to 5 year	Open-label study WA18696

\* ~ 50% pts on MTX alone

~ 50% pts on other DMARDs alone or in combination with MTX

\*\*At week 52 the primary endpoints are: change from baseline in modified Sharp total radiographic score and change in physical function.

Note - The following DMARDs were permitted for use in study WA18063: MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide.

IR=inadequate responder

The demographic and baseline disease characteristics of patients in these three studies were comparable (Table 8), which further justifies the pooling of these data as described in Section 6.4. This pooled population provides an overall description and estimate of the treatment effect of tocilizumab in the DMARD-inadequate responder population. In addition, this large population allows for comparisons where there are likely to be small differences between the treatment groups, including assessments in subpopulations of patients and a comparison of efficacy between the 4 mg/kg and 8 mg/kg tocilizumab groups, for which none of the individual studies were powered. Efficacy data for the pooled data set (DMARD-IR) are provided in the sections below.

As shown in Table 8, the patient population was typical of patients with moderate to severe RA, as demonstrated by a mean baseline DAS28 score of 6.7. Patients had a mean duration of RA of about 9 years and had previously been treated with at least one other DMARD (mean 1.6).

**Table 8 Baseline Demographic and Disease Characteristics – ITT Population**

	WA17822*	WA17823*	WA18063*	Pooled DMARD IR*
Female/Male (%)	85/15	82/18	81/19	82/18
Mean age in years	51	53	53	53
Mean duration of RA in years	7.5	9.3	9.8	9.3
RF Positive (%)	83	83	78	80
Mean DAS28	6.8	6.6	6.7	6.7
Mean number of SJC/TJC	20/32	17/29	20/30	19/30
CRP (mg/dL)	2.6	2.3	2.6	2.5
HAQ (mean)	1.6	1.5	1.5	1.5
Number of prior DMARDs	1.5	1.6	1.6	1.6
Oral CS/NSAIDs (%)	55/65	61/71	51/72	55/70
MTX dose (mean mg/wk)	14.5	15.4	14.7	15.0

\* 8 mg/kg tocilizumab arm

IR = inadequate responder; CS = corticosteroid

### 6.5.1.1 Patient Disposition

Most of the patients in the pooled DMARD IR population completed 24 weeks of treatment, either on their initial treatment or after having received escape therapy (Table 9). More patients in the tocilizumab groups withdrew for adverse events than patients in the placebo group. Conversely, more patients in the placebo group required escape therapy than patients in the tocilizumab groups, particularly compared to those treated with 8 mg/kg.

**Table 9 Summary of Patient Disposition – All Patients**

	Placebo + MTX N=1013 No. (%)	4 mg/kg TCZ + MTX N=615 No. (%)	8 mg/kg TCZ + DMARD N=1411 No. (%)
Completed 24 weeks (including ESCAPE)	915 (90)	559 (91)	1309 (93)
ESCAPE	263 (26)	98 (16)	79 (6)
Total Discontinued**	82 (8)	49 (8)	98 (7)
Adverse Events	19 (2)	29 (5)	63 (4)
Death	3 (<1)	0	2 (<1)
Lack of Efficacy	27 (3)	3 (<1)	4 (<1)
Failure to Return*	3 (<1)	2 (<1)	2 (<1)
Refused Treatment	22 (2)	13 (2)	25 (2)
Other	8 (<1)	4 (<1)	2 (<1)

\*Included “did not cooperate” and “withdrew consent.”

\*\*Excludes discontinuations on escape therapy.

### 6.5.1.2 Results from Individual Studies

All three studies met the primary endpoint (ACR20 response at week 24). Across all three studies, consistent results were observed for the primary and secondary endpoints. The greatest response was observed in the tocilizumab 8 mg/kg + DMARD group, particularly with respect to the more clinically relevant endpoints, with marked

improvements over placebo + DMARD in ACR50 response, ACR70 response, and DAS28 <2.6 ([Appendix 3](#)). Therefore, as described in Section [6.5.1](#), the following sections present efficacy data from the pooled DMARD IR population.

#### **6.5.1.3 ACR Response – Pooled Analysis**

Tocilizumab in combination with background DMARDs was more effective than DMARDs alone at reducing the signs and symptoms of active RA in patients who previously had an inadequate response to DMARDs. Treatment with tocilizumab every 4 weeks was statistically superior to treatment with DMARDs for ACR20, ACR50, and ACR70 responses at week 24 ([Table 10](#)). In addition, treatment with tocilizumab 8 mg/kg was superior to treatment with 4 mg/kg for all levels of ACR response ([Table 10](#)).



**Table 10 Summary and Analysis of the Percentage of Patients with an ACR20, ACR50 and ACR70 Response at Week 24 - 6 Month Pooled Data (ITT Population)**

	Placebo + DMARD (N=1010)	TCZ 4mg/kg+MTX (N=612)	TCZ 8mg/kg+DMARD (N=1406)
<b>ACR20</b>			
n	1010	612	1406
Responders	261 (25.8%)	304 (49.7%)	832 (59.2%)
p-value*		<.0001	<.0001
p-value**			0.0101
<b>ACR50</b>			
N	1010	612	1406
Responders	97 (9.6%)	167 (27.3%)	520 (37.0%)
p-value*		<.0001	<.0001
p-value**			0.0008
<b>ACR70</b>			
n	1010	612	1406
Responders	24 (2.4%)	70 (11.4%)	260 (18.5%)
p-value*		<.0001	<.0001
p-value**			0.0263

\*Comparison to placebo + DMARD

\*\*Comparison to TCZ 4 mg/kg + MTX

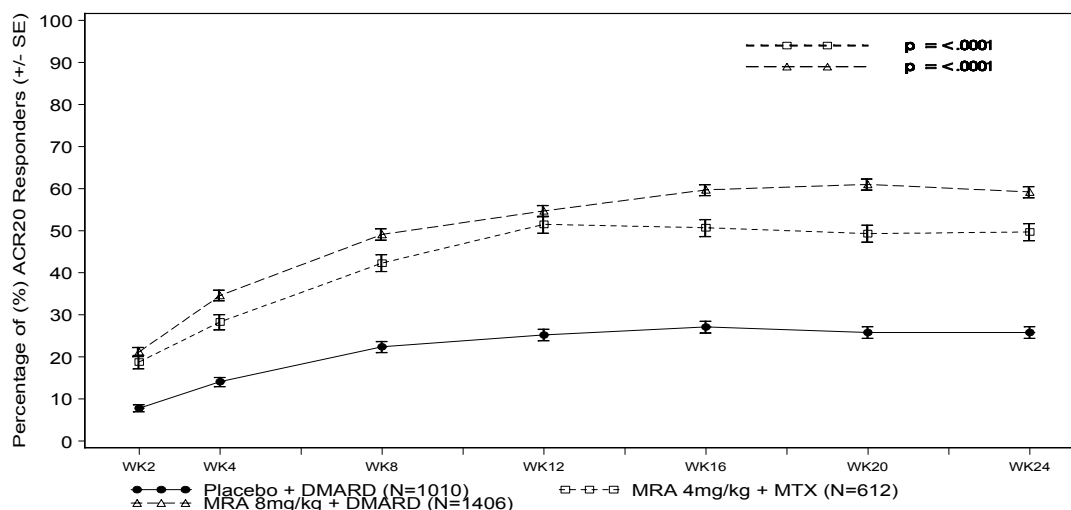
The stratification factor study is included in the model. Cochran-Mantel-Haenszel analysis was used to calculate p-values.

LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP was used primarily for the calculation of the ACR response; if missing, ESR was substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non-Responder'. TCZ 4 mg/kg + MTX pooled data from WA17822 and WA17823. TCZ 8 mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063.

The onset of action of tocilizumab was rapid, with evidence of ACR responses as early as week 2 that continued through week 24 ([Figure 8](#), [Figure 9](#), and [Appendix 4](#)). The highest ACR20, ACR50, and ACR70 responses over time were observed in patients treated with 8 mg/kg of tocilizumab + DMARDs.

**Figure 8 ACR20 Response Rates by Visit – DMARD IR, ITT Population**

EGacr20pli ACR20 Response Rates by Visit - 6 Month Pooled Data (ITT Population)

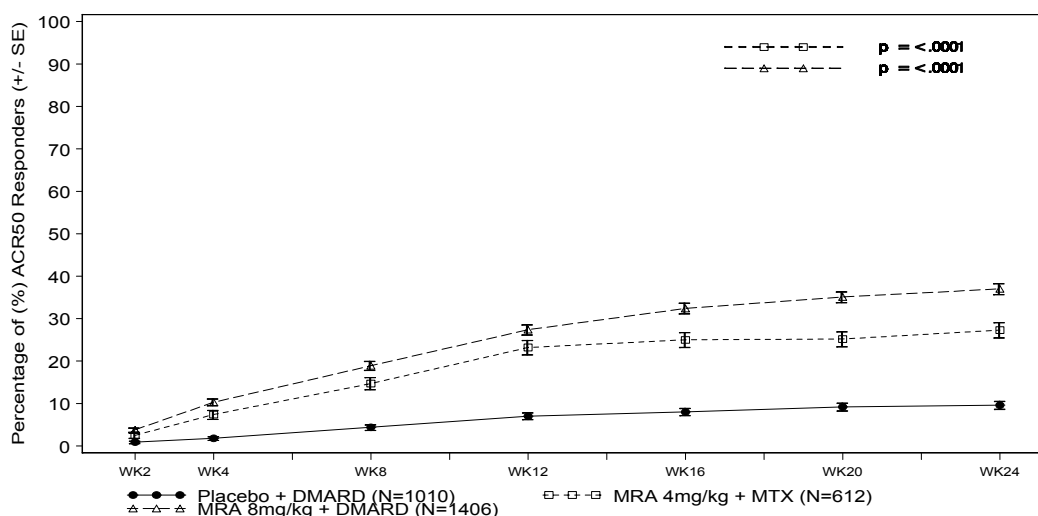


Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons to placebo + DMARD. LOCF used for joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

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**Figure 9 ACR50 Response Rates by Visit – DMARD IR, ITT Population**

EGacr50pli ACR50 Response Rates by Visit- 6 Month Pooled Data (ITT Population)



Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons to placebo + DMARD. LOCF used for joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

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In addition to the overall improvements in ACR, tocilizumab treatment resulted in improvements from baseline in all ACR core set components (tender joint count [TJC], swollen joint count [SJC], patient's global assessment of disease activity, physician's

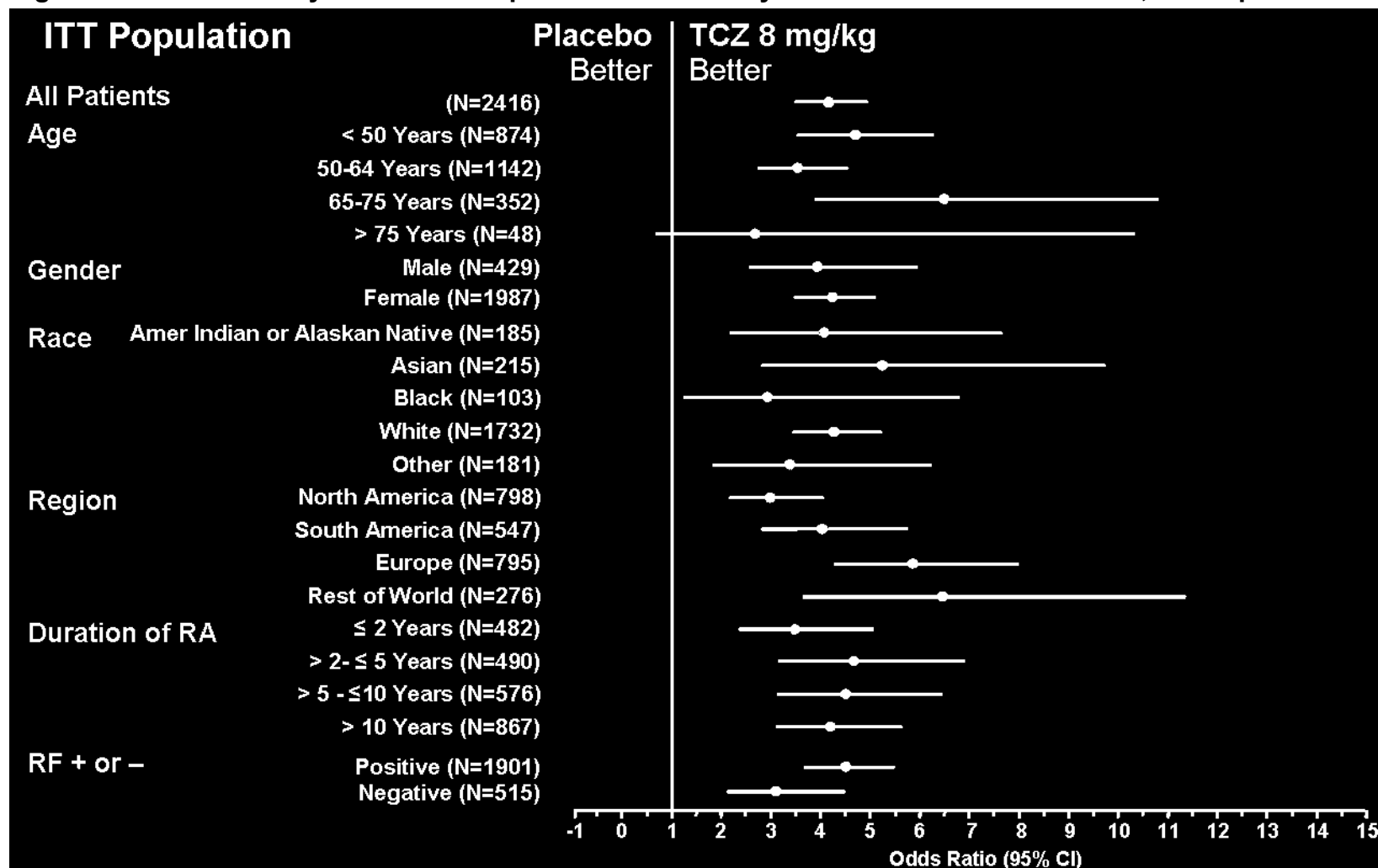
global assessment of disease activity, patient's pain assessment, HAQ-DI, CRP, and erythrocyte sedimentation rate [ESR]; [Appendix 5](#)).

ACR responses were consistent across subpopulations of patients. Clinically relevant improvements were evident regardless of the background DMARD regimen added to tocilizumab (WA18063 study only; [Table 11](#)). In addition, the proportion of patients achieving an ACR20 response was consistently higher among patients treated with tocilizumab than patients treated with placebo across all major demographic and clinical subgroups examined ([Figure 10](#)).

**Table 11 Summary of the Percentage of Patients with an ACR20 Response at Week 24 by Background DMARD Medication - WA18063 Study (ITT Population)**

	Placebo + DMARD		TCZ 8 mg/kg + DMARD	
	N	ACR20 Responders No. (%)	N	ACR20 Responders No. (%)
No DMARD	5	0	9	5 (55.6%)
One DMARD:				
MTX	224	56 (25%)	456	269 (59%)
Leflunomide	50	9 (18%)	78	51 (65.4%)
Sulfasalazine	16	0	35	23 (65.7%)
Chloroquine/ Hydroxychloroquine	17	5 (29.4%)	33	21 (63.6%)
Azathioprine	4	0	12	4 (33.3%)
Parenteral Gold	0	-	2	0
Two DMARDs	82	24 (29.3%)	152	100 (65.8%)
Three or more DMARDs	15	7 (46.7%)	26	15 (57.7%)
<b>Total ITT population</b>	<b>413</b>	<b>101 (24.5%)</b>	<b>803</b>	<b>488 (60.8%)</b>

**Figure 10** Summary of ACR20 Response at Week 24 by Intrinsic Factor – DMARD IR, ITT Population



### 6.5.1.4 DAS28 – Low Disease Activity and Remission

A DAS28 score of  $\leq 3.2$  represents low disease activity and a score  $< 2.6$  indicates DAS28 remission, according to EULAR criteria.

Approximately half of the patients treated with 8 mg/kg tocilizumab + DMARD achieved low disease activity and, importantly, one third achieved DAS28 remission (Table 12). There was a highly statistically significant difference between both tocilizumab treatment groups and the placebo + DMARD group ( $p < 0.0001$ ) at week 24. In addition, treatment with tocilizumab 8 mg/kg was superior to treatment with 4 mg/kg for DAS28 remission.

**Table 12** Summary and Analysis of the Percentage of Patients with Low Disease Activity (DAS28  $\leq 3.2$ ) and DAS28 Remission (DAS28  $< 2.6$ ) – Pooled DMARD IR, ITT Population

	Pooled DMARD Inadequate Responders N=3028		
	Placebo + DMARD N=655	TCZ 4 mg/kg + MTX N=460	TCZ 8mg/kg + DMARD N=1202
<b>Low Disease Activity</b>			
Responders	48 (7.3%)	145 (31.5%)	567 (47.2%)
p-value*		$< 0.0001$	$< 0.0001$
<b>DAS28 Remission</b>			
Responders	20 (3.1%)	75 (16.3%)	368 (30.6%)
p-value*		$< 0.0001$	$< 0.0001$
p-value**			$< 0.0001$

Sources: etsumdas28poolwk24ldai and etsumdas28poolwk24remi

\*Comparison to placebo + DMARD

\*\*Comparison to TCZ 4 mg/kg + MTX

### 6.5.1.5 Quality of Life

The short form-36 (SF-36) survey, which covers eight health dimensions including four physical domains (physical function, role-physical, bodily pain, and general health) and four mental domains (vitality, social function, role-emotional, and mental health), was used to assess the impact of tocilizumab on quality of life in accordance with FDA guidance. Tocilizumab was significantly more effective than control in improving the SF-36 physical and mental component summary scores at week 24 (Table 13 and Table 14). For both component scores, the difference in treatment effect between placebo + DMARD was higher in the tocilizumab 8 mg/kg + DMARD group compared with the tocilizumab 4 mg/kg + MTX group.

**Table 13      Analysis of Variance of Change from Baseline in SF-36 Physical Component Summary Score to Week 24: DMARD IR, ITT Population**

	Placebo + DMARD (N=1010)	TCZ 4mg/kg+MTX (N=612)	TCZ 8mg/kg+DMARD (N=1406)
n	620	422	1142
Adjusted Mean	4.79	8.76	9.12
Difference		3.98	4.33
95% CI for difference		(2.83, 5.13)	(3.48, 5.19)
p-value		<.0001	<.0001

The stratification factor study is included in the model. All comparison(s) to placebo + DMARD. No imputation used for missing score. All assessments are set to missing from the time a patient receives escape therapy. The norm based scores are reported in this table. Positive change indicates a better health state. TCZ 4 mg/kg + MTX pooled data from WA17822 and WA17823. TCZ 8 mg/kg + DMARD pooled data from WA17822, WA17823, and WA18063.

**Table 14      Analysis of Variance of Change from Baseline in SF-36 Mental Component Summary Score to Week 24: DMARD IR, ITT Population**

	Placebo + DMARD (N=1010)	TCZ 4mg/kg+MTX (N=612)	TCZ 8mg/kg+DMARD (N=1406)
n	620	422	1142
Adjusted Mean	2.86	4.98	6.03
Difference		2.12	3.17
95% CI for difference		(0.61, 3.63)	(2.05, 4.29)
p-value		0.0060	<.0001

The stratification factor study is included in the model. All comparison(s) to placebo + DMARD. No imputation used for missing score. All assessments are set to missing from the time a patient receives escape therapy. The norm based scores are reported in this table. Positive change indicates a better health state. TCZ 4 mg/kg + MTX pooled data from WA17822 and WA17823. TCZ 8 mg/kg + DMARD pooled data from WA17822, WA17823, and WA18063.

### **6.5.1.6      Sustained Efficacy**

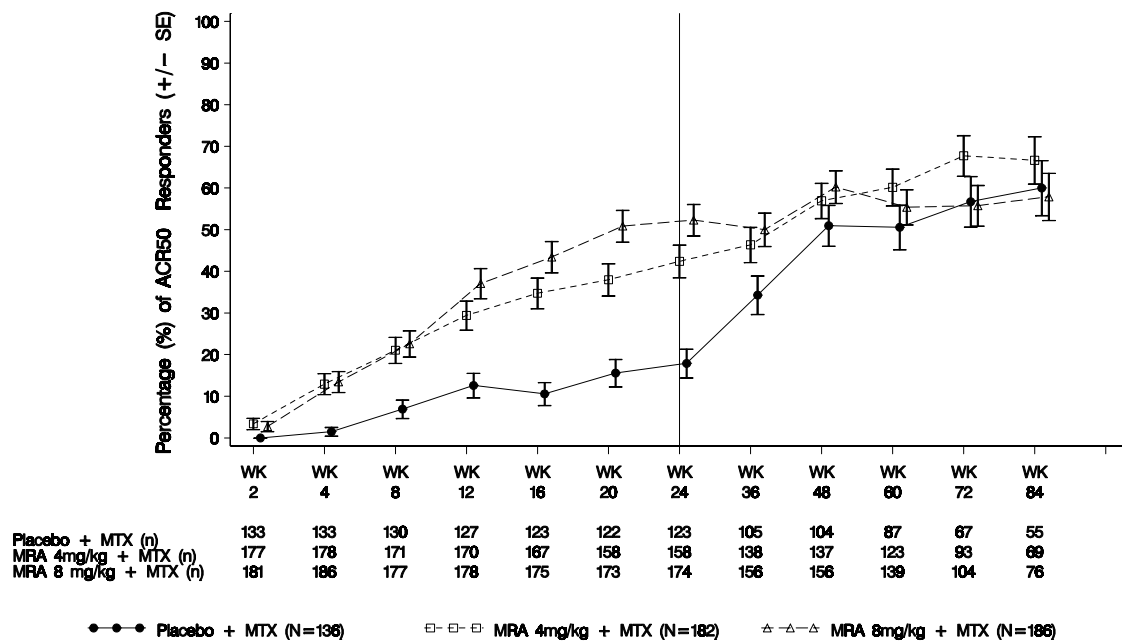
As described in Section 6.4, data from the double-blind, 24-week studies were combined with data from the open-label, extension studies to provide a long-term overview of efficacy per double-blind study. Overall response rates to therapy with tocilizumab 8 mg/kg + DMARD were maintained with continued treatment (Figure 11 and Figure 12). In addition, patients who were randomized to placebo or tocilizumab 4 mg/kg in the 24-week, double-blind studies and then switched to 8 mg/kg open-label therapy in the extension studies had an improvement in their disease activity shortly after switching

treatments. It should be noted that the number of patients is decreasing over time because these are ongoing studies and many patients have not yet reached the later time points.

DAS28 and EULAR scores were also maintained with continued treatment ([Appendix 6](#) and [Appendix 7](#)).

**Figure 11 ACR50 Response Rates by Visit – WA17822 Study Group (ITT Population)**

EGpacm50wa17822 Plot of ACR50 Response Rates by Visit – WA17822 Study Group (ITT Population)

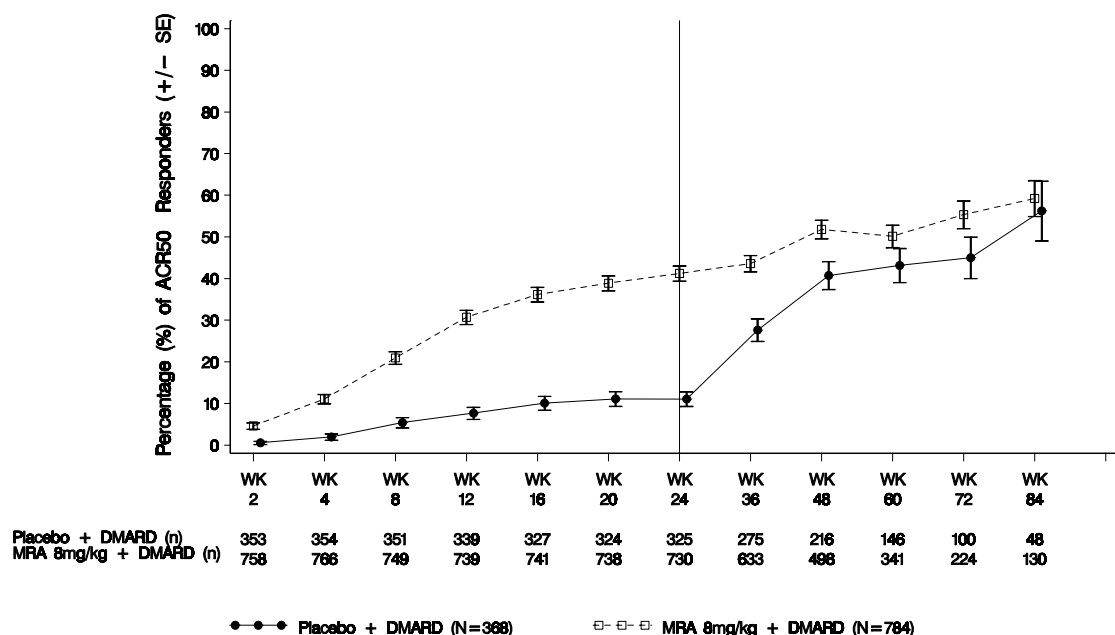


LOCF used for tender and swollen joint counts, no imputation used for HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily, however if the change in CRP is not calculable, the change in ESR is used if available. Escape patients are excluded.

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**Figure 12 ACR50 Response Rates by Visit – WA18063 Study Group (ITT Population)**

EGpacm50wa18063i Plot of ACR50 Response Rates by Visit – WA18063 Study Group (ITT Population)



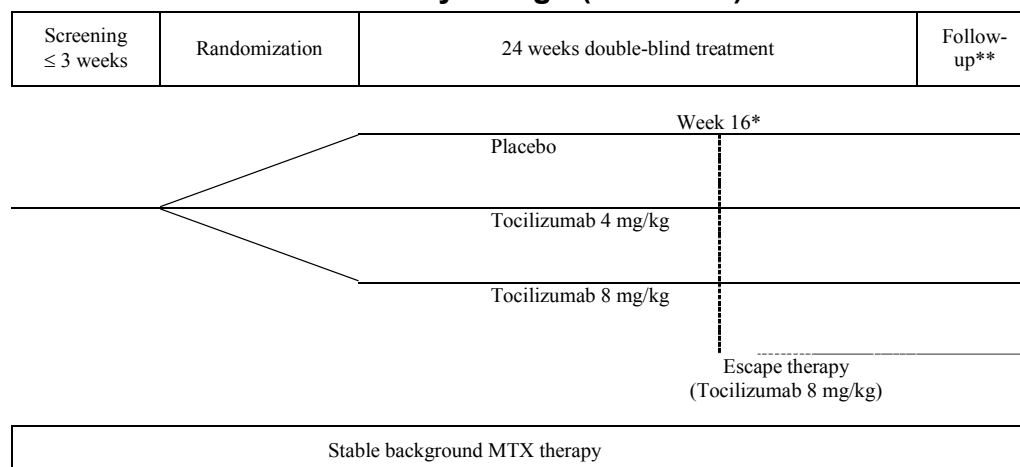
LOCF used for tender and swollen joint counts, no imputation used for HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily, however if the change in CRP is not calculable, the change in ESR is used if available. Escape patients are excluded.

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## 6.5.2 Patients with an Inadequate Response to Anti-TNF Therapy

Study WA18062 was a randomized, double-blind, placebo-controlled, parallel group study in adult patients with moderately to severely RA who had previously experienced an inadequate clinical response to previous anti-TNF therapy. Patients were randomly assigned in a 1:1:1 ratio to receive placebo, tocilizumab 4 mg/kg, or tocilizumab 8 mg/kg by IV infusion in combination with MTX at a stable dose of 10 to 25 mg/week (Figure 13).



**Figure 13 Overview of Study Design (WA18062)**

\*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 WA18696 returned for safety follow-up assessments 8 and 12 weeks after the last infusion of study treatment.

The demographic and baseline disease characteristics of patients in the three treatment groups was comparable (Table 15). The mean duration of RA was at least 11 years across the treatment groups and patients had a high degree of baseline disease activity, as indicated by the DAS28 score and the mean number of SJC and TJC, despite concurrent treatment with MTX (approximate dose of 16 mg/week).

**Table 15 Baseline Demographic and Disease Characteristics: Anti-TNF IR (WA18062)**

	Placebo + MTX N = 158	TCZ 4 mg/kg + MTX N = 161	TCZ 8 mg/kg +MTX N = 170
Female/Male (%)	79/21	81/19	84/16
Mean age in years	53	51	54
Mean duration of RA in years	11.4	11.0	12.6
RF positive (%)	75	73	79
Mean DAS28	6.8	6.8	6.8
Mean number of SJC/TJC	19/30	20/31	19/32
CRP (mg/dL)	3.7	3.1	2.8
HAQ (mean)	1.7	1.7	1.7
Number of prior DMARDs	2.1	2.0	1.9
Oral CS/NSAIDs (%)	58/58	58/62	52/62
MTX dose (mean mg/wk)	16.5	16.2	15.7

CS = corticosteroid

Patients were required to have previously received treatment with at least one anti-TNF agent and failed to respond or discontinued treatment due to safety or tolerability within 1 year of randomization into the study. Over half of the patients had failed at least one

anti-TNF treatments prior to entering this study. Few patients failed a previous anti-TNF treatment due to toxicity alone (Table 16).

**Table 16 Proportion of Patients who Failed 1, 2, or 3 Anti-TNF Therapies due to Inadequate Efficacy or Toxicity: Anti-TNF-Inadequate Responders (WA18062)**

	Placebo + MTX N = 158 %	TCZ 4 mg/kg + MTX N = 161 %	TCZ 8 mg/kg + MTX N = 170 %
1 Anti-TNF	48	50	53
2 Anti-TNFs	40	37	32
3 Anti-TNFs	12	12	15
Proportion failed due to			
Toxicity*	3	4	7
Inadequate efficacy**	82	80	78
Toxicity and inadequate efficacy	15	15	15
Time since discontinuation			
Median days prior to study start	84	75	84

\*Minimum treatment requirement of at least one complete dose.

\*\*Inadequate efficacy was defined in the protocol as: etanercept  $\geq 3$  months at 25 mg twice a week (or 50 mg weekly), at least four infusions of infliximab at  $\geq 3$  mg/kg, or adalimumab at a minimum of 40 mg every other week for  $\geq 3$  months.

Most of the patients completed 24 weeks of treatment, either on their initial treatment or escape therapy (Table 17). More than twice as many patients in the placebo group required escape therapy compared with the tocilizumab groups.

**Table 17 Summary of Patient Disposition: Anti-TNF-Inadequate Responders (WA18062)**

	Placebo + MTX N = 158 No. (%)	TCZ 4 mg/kg + MTX N = 161 No. (%)	TCZ 8 mg/kg + MTX N = 170 No. (%)
Completed 24 weeks (including ESCAPE)	127 (79)	138 (85)	152 (87)
ESCAPE	66 (41)	31 (19)	20 (11)
Total discontinued*	30 (19)	24 (15)	23 (13)
Adverse events	8 (5)	10 (6)	11 (6)
Death	0	0	0
Lack of efficacy	18 (11)	5 (3)	4 (2)
Failure to return	0	4 (2)	1 (<1)
Refused treatment	4 (3)	2 (1)	4 (2)
Violation of entry criteria/other violation	0	3 (2)	3 (2)

\*Excludes discontinuations on escape therapy

#### 6.5.2.1 ACR Response

Tocilizumab in combination with MTX was more effective than MTX alone at reducing the signs and symptoms of active RA in a population of treatment-recalcitrant patients who had failed to respond adequately to prior treatment with at least one TNF-antagonist. Treatment with tocilizumab 8 mg/kg in combination with MTX was statistically and

clinically superior over treatment with placebo + MTX for ACR20, ACR50, and ACR70 responses at week 24 and numerically superior to treatment with tocilizumab 4 mg/kg ([Table 18](#)).

**Table 18      Summary and Analysis of the Percentage of Patients with an ACR20, ACR50 and ACR70 Response at Week 24: Anti-TNF IR, ITT Population (WA18062)**

	Placebo + MTX (N=158)	TCZ 4mg/kg + MTX (N=161)	TCZ 8mg/kg + MTX (N=170)
<b>ACR20</b>			
n	158	161	170
Responders	16 (10.1%)	49 (30.4%)	85 (50.0%)
p-value		<.0001	<.0001
<b>ACR50</b>			
n	158	161	170
Responders	6 (3.8%)	27 (16.8%)	49 (28.8%)
p-value		<.0001*	<.0001
<b>ACR70</b>			
n	158	161	170
Responders	2 (1.3%)	8 (5.0%)	21 (12.4%)
p-value		0.1005	0.0002

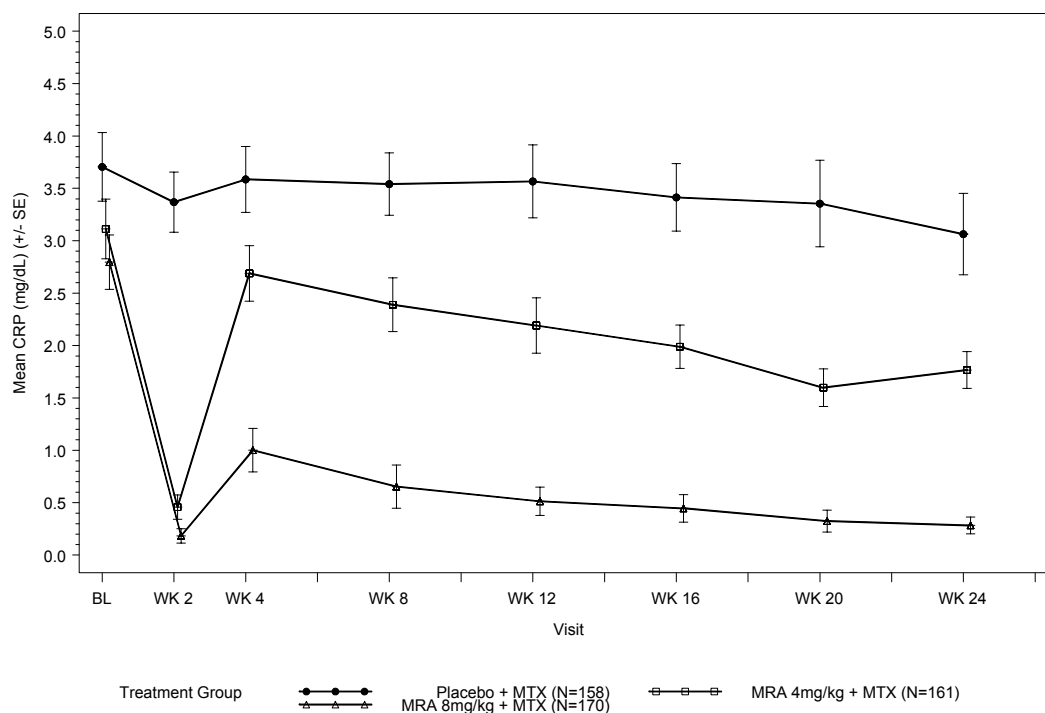
Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons to placebo + MTX. LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR, and VAS assessments. CRP was used primarily for the calculation of the ACR response; if missing, ESR was substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non-Responder'. Analysis stratified by site.

\* Due to a break in the hierarchical testing of the secondary endpoints, this cannot be considered as statistically significant.

In addition to the overall improvements in ACR, tocilizumab treatment resulted in improvements in all ACR core set components (TJC, SJC, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's pain assessment, HAQ-DI, CRP, and ESR) with the greatest improvements observed in the tocilizumab 8 mg/kg + MTX group ([Figure 14](#) and [Appendix 8](#)). Notably, the tocilizumab 4 mg/kg + MTX group did not demonstrate suppression of CRP over the entire dosing interval.

**Figure 14 Mean CRP (mg/dL) by Visit: Anti-TNF IR, ITT Population (WA18062)**

efmeansevascrpi Plot of Mean C-Reactive Protein (mg/dL) by Visit (ITT Population)



No imputation used for missing data

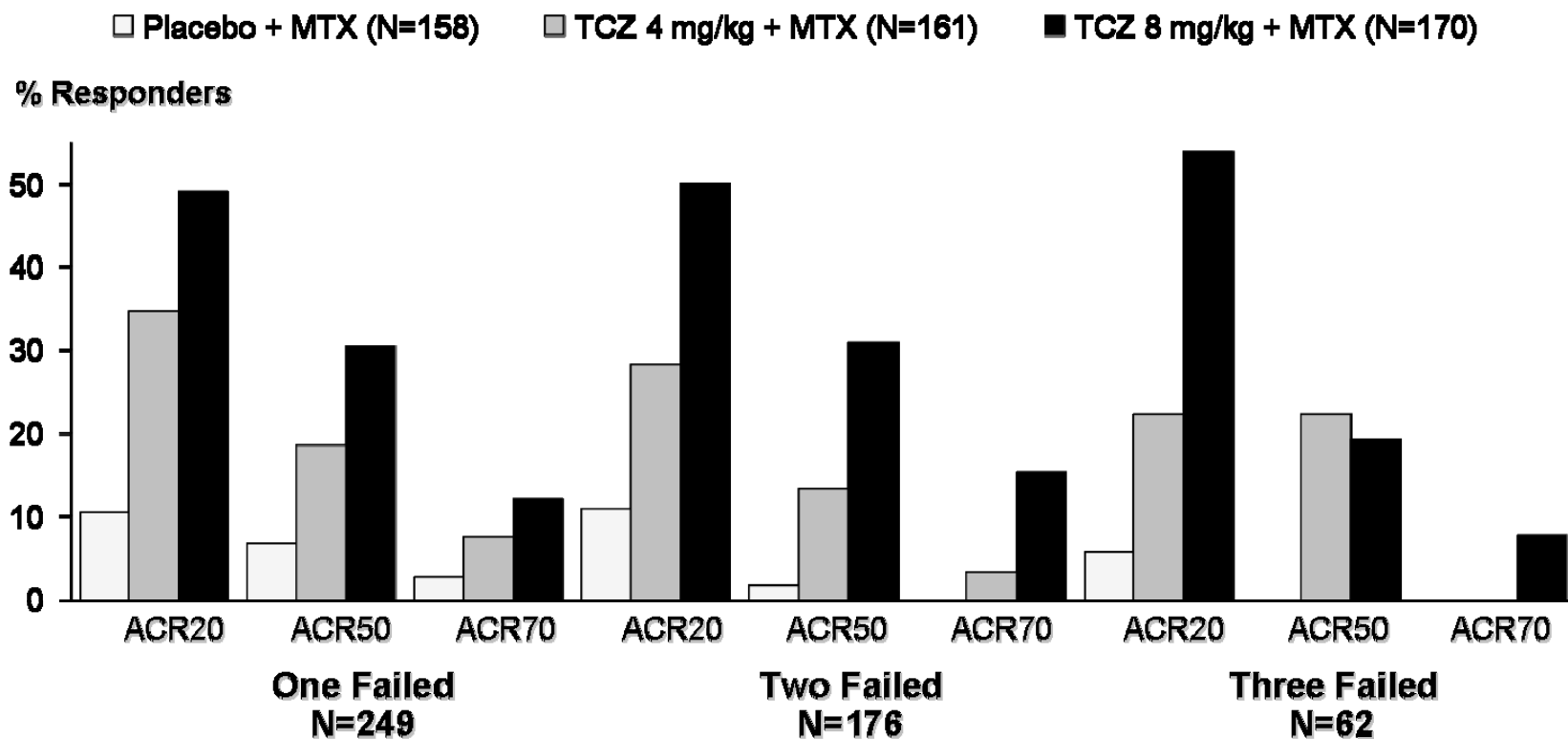
All assessments are set to missing from the time a patient receives escape therapy.

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As with patients who were DMARD IRs, the onset of action of tocilizumab was rapid, with evidence of ACR responses as early as week 2 that continued through week 24 ([Appendix 9](#), [Appendix 10](#), and [Appendix 11](#)). The highest ACR20, ACR50, and ACR70 responses over time were observed in patients treated with 8 mg/kg of tocilizumab + MTX.

There were no discernible differences between the proportions of ACR20 responders in patients who had failed one anti-TNF compared with those who had failed two or three anti-TNFs for the tocilizumab 8 mg/kg + MTX group ([Figure 15](#)). However, the proportion of patients achieving ACR50 and ACR70 responses was lowest among patients who failed three anti-TNF therapies compared with those who failed one or two previous therapies.

**Figure 15** Anti-TNF IR: ACR20, ACR50, ACR70 Response at Week 24 by Number of Previously Failed Anti-TNFs (WA18062)



### 6.5.2.2 DAS28 – Low Disease Activity and Remission

As with the DMARD IRs, approximately half of the anti-TNF IRs who were treated with 8 mg/kg tocilizumab + MTX achieved low disease activity and, importantly, one third achieved DAS28 remission (Table 19). There was a highly statistically significant difference between the tocilizumab 8 mg/kg treatment group and the placebo + MTX group ( $p=0.0001$ ) at week 24.

**Table 19** Summary and Analysis of the Percentage of Patients with Low Disease Activity ( $\text{DAS28} \leq 3.2$ ) and DAS28 Remission ( $\text{DAS28} < 2.6$ ) – Anti-TNF IR, ITT Population (WA18062)

	Anti-TNF Inadequate Responders N=489		
	Placebo + MTX n=61	TCZ 4 mg/kg + MTX n=105	TCZ 8mg/kg + MTX n=123
Low Disease Activity Responders	3 (4.9%)	16 (15.2%)	63 (51.2%)
DAS28 Remission Responders	1 (1.6%)	8 (7.6%)	37 (30.1%)
p-value*		0.0533	0.0001

### 6.5.2.3 Quality of Life

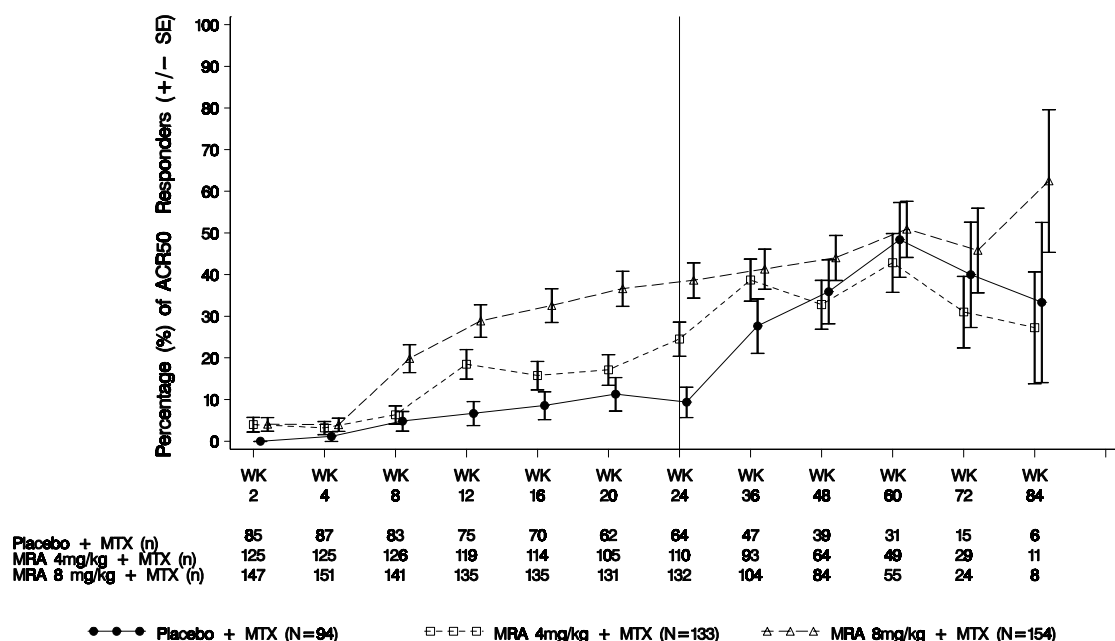
In the anti-TNF IR population, tocilizumab 8 mg/kg was significantly more effective than control in improving the SF-36 physical component score at week 24. Greater improvements in the tocilizumab groups compared with the placebo + MTX group were also seen for the SF-36 mental component score at week 24, but the differences did not achieve statistical significance (Appendix 12 and Appendix 13).

### 6.5.2.4 Sustained Efficacy

Overall response rates to therapy with tocilizumab 8 mg/kg + MTX were maintained with continued treatment (ACR50 response; Figure 16). In addition, patients who were randomized to placebo or tocilizumab 4 mg/kg in the 24-week, double-blind studies and then switched to 8 mg/kg open-label therapy in the extension studies had an improvement in their disease activity shortly after switching treatments.

**Figure 16 ACR50 Response Rates by Visit – WA18062 Study Group (ITT Population)**

EGpacm50wa18062l Plot of ACR50 Response Rates by Visit – WA18062 Study Group (ITT Population)



LOCF used for tender and swollen joint counts, no imputation used for HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily, however if the change in CRP is not calculable, the change in ESR is used if available. Escape patients are excluded.

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## 6.6 Efficacy in Monotherapy

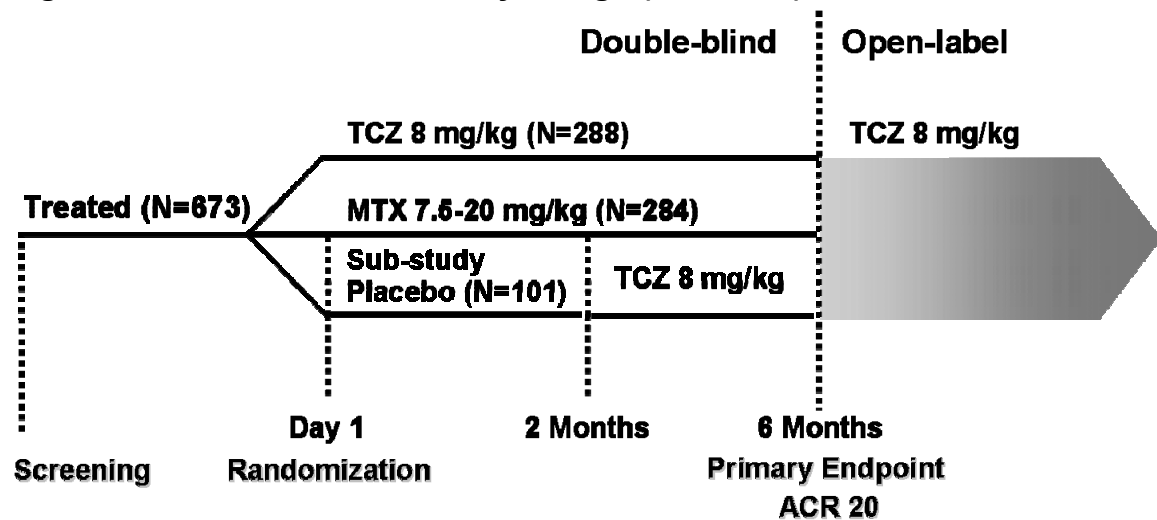
WA17824 was a study in adult patients with moderately to severely RA who had not been treated with MTX within the 6 months before randomization and who had not discontinued MTX as a result of clinically important toxic effects or lack of response (Figure 17). All DMARDs had to have been discontinued prior to study entry. Patients were randomly assigned in a double-blind, double-dummy fashion to either tocilizumab 8 mg/kg every 4 weeks or to MTX oral capsules weekly. MTX was administered in an escalating dose regimen, with the initial dose of 7.5 mg increasing to 15 mg at week 4 and to 20 mg at week 8.

The study was designed to demonstrate non-inferiority against MTX. As an internal control to confirm that both active treatment arms were effective, the study also included a placebo controlled substudy, where patients at selected sites in the US, Canada, and Israel were randomized (1:1:1) to the previously described groups and a placebo group. In the placebo group, patients received MTX placebo and tocilizumab placebo for 8 weeks; from week 8, the placebo infusion was replaced by a tocilizumab 8 mg/kg infusion for the remaining 16 weeks of the study. Patients taking part in the placebo-controlled substudy who did not experience a 20% decrease from baseline in SJC and TJC before week 8 could receive escape therapy with tocilizumab 8 mg/kg.



This study also included a “transition phase.” Patients who were responding well to their blinded treatment regimen could either continue their treatment in the blinded transition phase or enter the open-label, long-term extension study, WA18696, in which they could receive open-label tocilizumab therapy for up to 5 years. Patients entering the transition phase of WA17824 continued to receive the same blinded treatment that they received in the core study until the last patient enrolled completed their last visit in the double-blind period of the study and the database was locked. During the transition phase, patients could still decide to go into the extension study at any time and for any reason. Patients in the transition phase could also enter the extension study once the WA17824 database was locked and the study was unblinded.

**Figure 17 Overview of Study Design (WA17824)**



The treatment groups were well balanced with respect to demographic characteristics and baseline clinical RA characteristics (Table 20). Mean disease duration was approximately 6 years, reflecting a relatively early RA population. Indeed, when patients were further stratified by disease duration, over 40% had a RA disease duration of < 2 years. Moreover, 66% of patients in each treatment group were MTX-naïve and approximately 43% of patients were completely DMARD-naïve. However, patients had a high degree of disease activity at baseline, as reflected by mean DAS28 score, mean SJC and TJC, and baseline CRP and ESR levels.

**Table 20 Baseline Demographic and Disease Characteristics: Monotherapy Study (WA17824) (ITT Population)**

	MTX N = 284	TCZ 8 mg/kg N = 286
Female/Male	79/21	83/17
Mean age in years	50	51
Mean duration of RA in years	6.3	6.4
Duration of RA < 2 years (%)*	125 (44)	117 (41)
RF positive (%)	75	74
Mean DAS28	6.8	6.8
Mean number of SJC/TJC	19/31	19/32
CRP (mg/dL)	3.1	3.0
HAQ (mean)	1.5	1.6
Number of prior DMARDs	1.1	1.2
Oral corticosteroids/NSAIDs (%)	47/77	48/80
MTX/DMARD naïve (%)	67/45	67/40

\*Safety Population

The majority of patients (82.6%) in the MTX group were more than 80% compliant with the MTX dosing regimen and the mean and median MTX dose from baseline to week 24 was 15.5 mg and 16.9 mg, respectively.

Most of the patients in both treatment groups completed 24 weeks of treatment, either on their initial treatment or after having received escape therapy ([Table 21](#)). More patients in the MTX group than in the tocilizumab group received escape therapy or withdrew for adverse events.

**Table 21 Summary of Patient Disposition: Monotherapy Study (WA17824)**

	MTX N = 284	TCZ 8 mg/kg N = 288
Completed 24 weeks (including ESCAPE)	262 (92%)	268 (93%)
ESCAPE	11	7
Total discontinued*	22 (8)	19 (7)
Adverse events	10 (4)	5 (2)
Death	1 (<1)	3 (1)
Lack of efficacy	3 (1)	1 (<1)
Failure to return	1 (<1)	4 (1)
Refused treatment	7 (3)	6 (2)

\* Excludes discontinuations on escape therapy

### 6.6.1 ACR Response

Tocilizumab was more effective than MTX at reducing the signs and symptoms of active RA in patients who were primarily naïve to MTX treatment. Those patients in the study who had previously received MTX had not failed treatment for lack of efficacy or discontinued for safety reasons.

As per study design, treatment with tocilizumab 8 mg/kg every 4 weeks was first demonstrated to be non-inferior and then, subsequently, statistically superior to treatment with MTX for ACR20, ACR50, and ACR70 responses at week 24 ([Table 22](#)).

**Table 22      Summary and Analysis of the Percentage of Patients with an ACR20, ACR50 and ACR70 Response at Week 24 – Monotherapy Study (WA17824) (ITT Population)**

	MTX (N=284)	TCZ 8mg/kg (N=286)
<b>ACR20</b>		
n	284	286
Responders	149 (52.5%)	200 (69.9%)
Weighted difference vs. MTX		0.19
95% C.I. of weighted difference		( 0.11, 0.27)
p-value		<.0001
<b>ACR50</b>		
n	284	286
Responders	95 (33.5%)	126 (44.1%)
Weighted difference vs. MTX		0.12
95% C.I. of weighted difference		( 0.04, 0.20)
p-value		0.0023
<b>ACR70</b>		
n	284	286
Responders	43 (15.1%)	80 (28.0%)
Weighted difference vs. MTX		0.14
95% C.I. of weighted difference		( 0.07, 0.22)
p-value		0.0002

Analysis stratified by site and disease duration.

LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP was used primarily for the calculation of the ACR response, if missing, ESR was substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated were set to 'Non-Responder'.

This study included a placebo arm with the substudy as an internal control. The results of the analysis of the treatment difference between tocilizumab and placebo at Week 8 showed that tocilizumab was superior to placebo, further supporting the trial design and result of the primary analysis ([Table 23](#)).

**Table 23      Summary and Analysis of the Percentage of Patients with an ACR20 Response at Week 8 Monotherapy Study (WA17824) (ITT Population)**

	Placebo/TCZ (N=99)	TCZ 8mg/kg (N=286)
ACR20		
n	99	286
Responders	13 (13.1%)	159 (55.6%)
Weighted difference vs. Placebo		0.43
95% C.I. of weighted difference		( 0.34, 0.52)*

\* Statistical significance demonstrated if lower limit of 95% CI TCZ minus placebo > 0.

Analysis stratified by disease duration. LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP was used primarily for the calculation of the ACR response, if missing, ESR was substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non-Responder'. Placebo/TCZ patients have only received Placebo medication up to the Week 8 analysis.

Treatment with 8 mg/kg of tocilizumab as monotherapy improved all ACR core set components (TJC, SJC, patient's and physician's global assessment of disease activity, patient's pain assessment, HAQ-DI, CRP, and ESR; [Appendix 14](#)).

The time to onset of response following administration of tocilizumab was rapid, with onset of action as early as week 2 ([Appendix 15](#)). The difference in response among patients treated with tocilizumab compared with MTX was also evident over time, where continued treatment with tocilizumab resulted in a continuous improvement in the level of response over the 24-week treatment period ([Appendix 16](#) and [Appendix 17](#)).

ACR responses were consistently superior with tocilizumab 8 mg/kg in a subgroup analysis of MTX-naïve and DMARD-naïve patients.

### **6.6.2      DAS28 – Low Disease Activity and Remission**

Improvements in disease activity were consistent with the symptomatic improvements assessed by the ACR variables. At week 24, approximately half of the patients treated with tocilizumab 8 mg/kg achieved low disease activity and approximately one third achieved DAS28 remission ( $\text{DAS28} \leq 2.6$ ), more than in the MTX group ([Table 24](#)).

**Table 24**      **Summary and Analysis of the Percentage of Patients with Low Disease Activity ( $\text{DAS28} \leq 3.2$ ) and DAS28 Remission ( $\text{DAS28} < 2.6$ ) – Monotherapy Study (WA17824) (PP Population)**

	<b>MTX N=228</b>	<b>TCZ 8 mg/kg N=236</b>
<b>Low Disease Activity</b>		
Responders	42 (18.4%)	104 (44.1%)
<b>DAS28 Remission</b>		
Responders	26 (11.4%)	75 (31.8%)
Odds ratio [95% CI]		3.839 [2.323; 6.344]

### **6.6.3      Quality of Life**

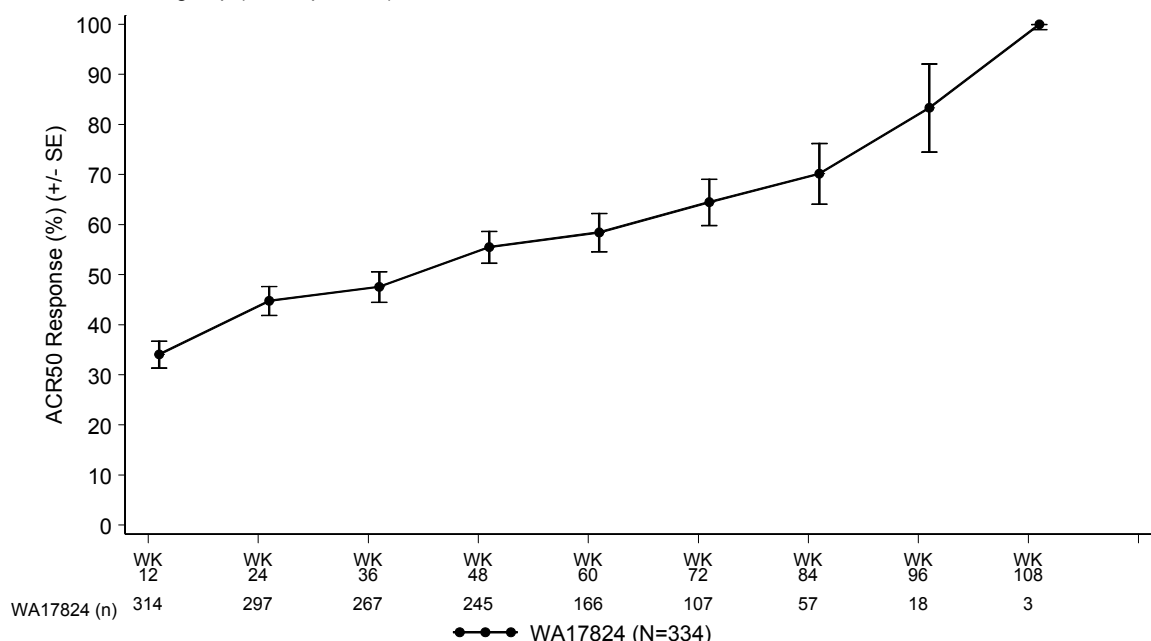
The mean change from baseline in physical component score, mental component score, and the individual domain scores at week 24 was higher in the tocilizumab 8 mg/kg group compared with the MTX group. The difference in the adjusted means between the tocilizumab group and the MTX group at week 24 was 2.01 (95% CI 0.37 to 3.65) in favor of tocilizumab for the physical component summary score and 1.96 (95% CI -0.31 to 4.23) for the mental component summary score.

### **6.6.4      Sustained Efficacy**

Patients who entered the open-label, long-term extension studies after completing the double-blind treatment period in study WA17824 could continue to receive tocilizumab 8 mg/kg as monotherapy. In the group of patients who remained on monotherapy, efficacy was maintained ([Figure 18](#)).

**Figure 18 ACR50 Response Rates by Visit – TCZ 8 mg/kg Monotherapy (WA17824)**

EGpACR1a5isbg01\_4msu Plot of ACR50 Response Rates by Visit - MRA 8 mg/kg Monotherapy Subgroup (ITT Population)



LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted.  
MRA 8 mg/kg monotherapy subgroup contains the patients that were receiving MRA 8 mg/kg monotherapy at the time of the data cut.

Program : \$PROD/cd11935l/p11935b/EGpACR1.sas  
Output : \$PROD/cd11935l/p11935b/reports/EGpACR1a5isbg01\_4msu.cgm  
21DEC2007 15:12

## 6.7 Efficacy Summary and Conclusions

The benefit of tocilizumab in treating the signs and symptoms of RA was confirmed in the clinical development program. Tocilizumab demonstrated consistent and robust effects on numerous pre-specified primary and the majority of secondary endpoints in a broad range of RA patients with moderately to severely active RA whether they started DMARD therapy de novo or required additional treatment following an inadequate response to previous treatment. The data demonstrate that the 8 mg/kg dose offers the most reliable and consistent efficacy in all populations investigated and was the only dose that effectively controlled inflammation throughout the 1-month dosing interval. When treated with this dose, substantial numbers of patients achieve a 50% or better ACR response, DAS28 remission, and low disease activity and/or a EULAR good response, which reflect clinically relevant improvements in signs and symptoms of the disease. The benefits of treatment were apparent rapidly following the start of tocilizumab therapy and the magnitude of response was maintained with continued duration of treatment. Responses obtained were sustained for at least two years. Therefore, Roche recommends the tocilizumab 8 mg/kg dose regimen for use in medical practice.

## **7. CLINICAL SAFETY**

The overall safety data in the tocilizumab development program demonstrate that:

- Tocilizumab was generally well tolerated as monotherapy and in combination with MTX or other non-biologic DMARDs.
- Many of the adverse events reported are consistent with the known mechanism of action of tocilizumab.
- The rates of serious infections in the double-blind trials were 3.75 events per 100 patient-years in the placebo/DMARD group, 4.35 in the tocilizumab 4 mg/kg + DMARD group, and 5.18 in the tocilizumab 8 mg/kg + DMARD group and these rates did not increase over time.
- In the Phase 3 double-blind program, 3 patients treated with tocilizumab and no patients in the comparator groups had GI perforations. Ten additional patients had GI perforations that occurred beyond 24 weeks.
- The observed decrease in neutrophils is dose-dependent, occurred largely within the normal range, and was reversible upon discontinuation of tocilizumab.
- LDL levels increased in both the tocilizumab 4 mg/kg and 8 mg/kg treatment groups and responded appropriately to statin therapy.
- Rates of myocardial infarction and stroke were similar across treatment groups in the double-blind studies and did not increase over time.
- Most ALT and AST elevations were transient and returned to normal without dose adjustment or treatment discontinuation. Elevated transaminases were not associated with abnormal liver function and no serious adverse events were associated with the transaminase elevations. In 4142 patient-years of exposure there were no patients who met the criteria of Hy's Law.
- In the 6-month, double-blind studies, the rate of malignant neoplasms was 1.33 events per 100 patient-years and 1.27 in the tocilizumab and control groups, respectively. Following longer-term treatment, the rate in the total Phase 3 population was 1.45 events per 100 patient-years; excluding non-melanoma skin cancers, the rate was 0.91 per 100 patient-years. Despite the low event rate, a potential risk for individual tumor types cannot be excluded at this time.
- Serious infusion reactions were uncommon; most of these events occurred after the second or third infusion of tocilizumab.
- Anti-tocilizumab antibody was detected in < 2% of patients. In general, the emergence of antibody was not associated with either loss of efficacy or a deterioration in the safety profile.

### **7.1 Introduction and Overview**

This section provides a summary of the safety data for tocilizumab when used alone or in combination with MTX or other DMARDs for the treatment of RA. The presentations of safety data are based on information submitted to the FDA in the clinical section of the BLA or in the 4MSU up to a clinical cutoff date of October 1, 2007 for general safety information and January 31, 2008 for serious adverse events and deaths.

The tocilizumab safety database includes the five double-blind, controlled studies and the two open-label, long-term extension studies (Table 3). The clinical safety database includes total of 3778 patients who received at least one dose of tocilizumab. Safety was assessed by collecting information on adverse events, deaths, serious adverse events, reasons for withdrawals, laboratory test, and vital signs. Events are reported by the preferred term per the investigator.

Safety data are presented as follows:

- General safety including adverse events, serious adverse events, deaths, and adverse events leading to treatment discontinuation.
- Adverse events of special interest including infection, GI perforation, malignancy, demyelinating disorders, cardiovascular risk, liver enzyme elevations, infusion reactions, and immunogenicity.

For the presentation and interpretation of data and to add precision for the detection of events occurring at a low frequency, data were pooled into two large populations:

**Double-blind studies:** Safety data from the double-blind studies are presented together. Data from the four double-blind studies where patients were treated with tocilizumab in combination with MTX or other DMARDs are pooled and presented in three treatment groups: tocilizumab 8 mg/kg + DMARDs, tocilizumab 4 mg/kg + MTX, and placebo + DMARDs. Data from the fifth double-blind study, the monotherapy study WA17824, are not pooled with the data from the combination trials as this study had a different treatment regimen, design, and included a different patient population. Data from this study are presented by the two treatment groups: tocilizumab 8 mg/kg and MTX.

As described in Section 4, patients in the double-blind, controlled studies who were not responding adequately to treatment by a certain time point could receive escape therapy. Data for patients who received tocilizumab as open-label, escape therapy are only included in the respective double-blind treatment groups up to the point of escape.

**Total Safety Exposure Group:** Long-term safety and tolerability of tocilizumab was assessed by combining patient data from the double-blind studies with data from the open-label extension studies. The data were analyzed from the time of initial exposure to tocilizumab. This data set includes all patients who received at least one dose of tocilizumab whether in the double-blind studies, the transition phase of study WA17824, the two open-label extension studies, or as escape therapy in the double-blind studies. Total safety exposure data are provided as rates per 100 patient-years and are presented in four groups: tocilizumab 4 mg/kg + DMARD, tocilizumab 8 mg (including combination therapy and monotherapy), control (including placebo, MTX, and DMARD), and all tocilizumab.

In addition to the safety data from these pooled populations, serious adverse events, deaths, and adverse events of special interest are provided from studies conducted by Roche's co-development partner, Chugai. These data are from RA studies unless otherwise specified. The data from Chugai are presented in a separate column in the Total Safety Exposure tables labeled "Chugai."



Any medically significant events that occurred after the clinical cut-off dates for the 4MSU are mentioned separately.

## **7.2 Exposure**

A total of 2644 patients received at least one dose of tocilizumab in the double-blind studies providing 1131.3 patient-years of exposure. This includes 288 patients treated with tocilizumab as monotherapy for a total exposure of 125.6 patient-years. The other 2356 patients received tocilizumab in combination with MTX or other DMARDs; 774 patients received 4 mg/kg for a total of 320.9 patient-years of exposure and 1582 received 8 mg/kg for a total of 684.7 patient-years of exposure.

Cumulatively, in the Total Safety Exposure group, 3778 patients have received at least one dose of tocilizumab providing a total of 4142 patient-years of exposure ([Table 25](#)). After 6 months, exposure is primarily from the 8 mg/kg group as this is the dose patients are receiving in the ongoing open-label extension studies. However, as patients were allowed to reduce their dose to 4 mg/kg for safety reasons, there are some exposure data in the 4 mg/kg dose group.

In the Chugai RA studies, 945 patients received at least one dose of tocilizumab, the majority of whom received 8 mg/kg tocilizumab monotherapy, providing a total of 2024.1 patient-years of exposure as of October 1, 2007.

**Table 25                      Summary of Exposure by Actually Received Treatment and Duration (Safety Population)**

	Duration of Exposure	Person	Person Time (years)
Exposure to TCZ	Total Exposure	3778	4141.5
	Cumulative up to 3 months	3474	798.9
	Cumulative up to 6 months	3183	1464.0
	Cumulative up to 9 months	2366	1632.4
	Cumulative up to 12 months	2121	1951.1
	Cumulative up to 15 months	1864	2143.4
	Cumulative up to 18 months	1463	2018.8
	Cumulative up to 21 months	1056	1700.0
	Cumulative up to 24 months	640	1177.5
	Cumulative up to 27 months	345	714.1
	Cumulative up to 30 months	113	259.9
	Cumulative up to 33 months	10	25.3
	Cumulative up to 36 months	1	2.8
Exposure to TCZ 4 MG*	Total Exposure	1181	434.9
	Cumulative up to 3 months	842	193.6
	Cumulative up to 6 months	546	251.1
	Cumulative up to 9 months	54	37.3
	Cumulative up to 12 months	24	22.1
	Cumulative up to 15 months	16	18.4
	Cumulative up to 18 months	4	5.5
	Cumulative up to 21 months	2	3.2
	Cumulative up to 24 months	1	1.8
	Cumulative up to 27 months	1	2.1
Exposure to TCZ 8 MG	Total Exposure	3242	3706.7
	Cumulative up to 3 months	3016	693.6
	Cumulative up to 6 months	2792	1284.2
	Cumulative up to 9 months	2287	1577.9
	Cumulative up to 12 months	2016	1854.6
	Cumulative up to 15 months	1752	2014.6
	Cumulative up to 18 months	1323	1825.6
	Cumulative up to 21 months	894	1439.2
	Cumulative up to 24 months	491	903.4
	Cumulative up to 27 months	234	484.3
	Cumulative up to 30 months	68	156.4
	Cumulative up to 33 months	8	20.2
	Cumulative up to 36 months	1	2.8

Extent of Exposure = Date of last dose + 28 days - date of first dose + 1

\*Includes all patients who had a single dose of 4 mg/kg as a result of dose reduction; the number of patients who were randomized to and received at least one dose of TCZ 4 mg/kg was 774 patients.

### 7.3 Safety Profile of Tocilizumab in Double-Blind Studies

The overview of the safety profile of tocilizumab from the double-blind studies is provided in [Table 26](#).

**Table 26 An Overview of Adverse Events and Deaths - Double-Blind Studies (Safety Population)**

Number of Patients	TCZ 8 mg/kg N=288	MTX N=284	TCZ 4 mg/kg + MTX N=774	TCZ 8 mg/kg + DMARD N=1582	Placebo +DMARD N=1170
Adverse events	230 (79.9%)	220 (77.5%)	547 (70.7%)	1134 (71.7%)	733 (62.6%)
Serious adverse events	11 (3.8%)	8 (2.8%)	46 (5.9%)	95 (6.0%)	62 (5.3%)
Adverse events leading to withdrawal	11 (3.8%)	15 (5.3%)	38 (4.9%)	74 (4.7%)	28 (2.4%)
Adverse events leading to dose modification	56 (19.4%)	63 (22.2%)	103 (13.3%)	194 (12.3%)	84 (7.2%)
Deaths	3 pt	1 pt	-	2 pt	4 pt

Most patients treated with tocilizumab 8 mg/kg monotherapy in the double-blind studies experienced at least one adverse event and the incidence was similar to that reported for patients treated with MTX monotherapy. The incidence of serious adverse events was slightly higher in the tocilizumab group and events leading to withdrawal or dose interruption were slightly higher in the MTX group.

When tocilizumab was given in combination with MTX or other DMARDs, the overall incidence of adverse events was higher in the tocilizumab 8 mg/kg + DMARD group compared with the placebo + DMARD group and similar to the incidence in the tocilizumab 4 mg/kg + MTX group ([Table 26](#)).

#### 7.3.1 Common Adverse Events

Tocilizumab, given as monotherapy or in combination with MTX or other DMARDs, was generally well tolerated. The most frequently reported (> 2%) adverse events occurring more commonly ( $\geq 1\%$ ) with tocilizumab than with MTX or other DMARDs in the double-blind studies are summarized in [Table 27](#).

**Table 27**      **Summary of Adverse Events Reported in > 2% of Tocilizumab-treated Patients and with  $\geq$  1% Difference to Control – Double-Blind Studies (Safety Population)**

	TCZ 8 mg/kg N = 288	MTX N = 284	TCZ 4 mg/kg + DMARD N = 774	TCZ 8 mg/kg + DMARD N = 1582	Placebo + DMARD N = 1170
<b>Preferred term</b>	<b>%</b>	<b>%</b>	<b>%</b>	<b>%</b>	<b>%</b>
URTI	7.3	5.3	7.8	6.2	6.1
Nasopharyngitis	6.9	6.0	5.6	4.3	4.4
Headache	7.3	2.5	5.3	5.8	3.4
Hypertension	5.6	2.1	4.4	4.1	2.7
Dizziness	3.1	1.4	3.1	1.9	1.7
Rash	2.4	1.4	3.3	3.9	1.3
Mouth ulceration	2.1	2.1	2.0	1.3	0.5
Gastritis	1.0	1.8	1.8	1.2	0.8
Increased transaminases*	8.3	8.8	5.9	5.0	4.5
Back pain	2.4	1.1	2.1	3.3	2.4
Cough	2.8	0.4	2.3	2.1	1.9
Pharyngolaryngeal pain	2.4	1.1	1.7	1.9	1.1
Bronchitis	3.1	2.1	3.2	4.3	3.2
Arthralgia	2.4	1.4	1.1	1.4	2.0

URTI = upper respiratory tract infection

\*Increased AST, increased ALT, ALT abnormal, transaminase increased

### 7.3.2 Serious Adverse Events

In the double-blind studies, the nature of adverse events reported reflected the patient population enrolled (Table 28). Infections and infestations were the most frequently reported serious adverse events and are discussed in more detail in Section 7.6.1.1. The frequency of serious adverse events in other system organ classes was comparable between patients treated with tocilizumab and patients treated with MTX or other DMARDs. Serious adverse events reported by at least two patients receiving tocilizumab in the double-blind controlled studies are summarized in Table 28. Serious adverse events that occurred in more than one patient in the comparator groups are not included unless they were also reported by more than one patient exposed to tocilizumab.

**Table 28                      Serious Adverse Events Reported by  $\geq 2$  Patients  
Receiving Tocilizumab in the Double-Blind Studies**

	TCZ 8 mg/kg N = 288	MTX N = 284	TCZ 4 mg/kg + DMARD N = 774	TCZ 8 mg/kg + DMARD N = 1582	Placebo + DMARD N = 1170
Preferred term	N (%)	N (%)	N (%)	N (%)	N (%)
<b>Infections</b>					
Pneumonia	2 (0.7)	2 (0.7)	6 (0.8)	9 (0.6)	4 (0.3)
Cellulitis	-	-	-	9 (0.6)	1 (0.1)
Herpes Zoster	-	-	-	5 (0.3)	-
Urinary tract infection	-	-	1 (0.1)	1 (0.1)	4 (0.3)
Sepsis	-	1 (0.3)	2 (0.3)	1 (0.1)	1 (0.1)
Gastroenteritis	-	-	3 (0.4)	-	-
Bronchitis	-	-	1 (0.1)	1 (0.1)	1 (0.1)
<b>Gastrointestinal</b>					
Diverticular perforation	-	-	-	2 (0.2)	-
Gastric Ulcer	1 (0.3)	-	-	1 (0.1)	-
Esophagitis	-	-	1 (0.1)	1 (0.1)	-
<b>Cardiac</b>					
Acute coronary syndrome / Myocardial Infarction	-	-	-	2 (0.1)	3 (0.3)
Coronary artery disease	-	-	-	2 (0.1)	-
<b>Central Nervous System</b>					
Carotid artery stenosis	-	-	2 (0.3)	1 (0.1)	-
Cerebrovascular accident	-	-	-	2 (0.1)	-
Hemorrhagic stroke	-	-	-	2 (0.1)	-
Syncope	-	-	2 (0.3)	-	-
<b>Injury</b>					
Fall	1 (0.3)	-	-	3 (0.2)	1 (0.1)
Femur fracture	-	-	1 (0.1)	2 (0.1)	-
Hip fracture	-	-	-	2 (0.1)	-
Spinal compression fracture	-	-	-	2 (0.1)	1 (0.1)
Tendon rupture	-	-	2 (0.3)	-	-
<b>Other</b>					
Pulmonary embolism	-	1 (0.3)	-	3 (0.2)	1 (0.1)
Interstitial lung disease	-	-	2 (0.3)	-	-
Back pain	-	-	-	3 (0.2)	1 (0.1)
Neutropenia	-	-	2 (0.3)	1 (0.1)	-
Nephrolithiasis	-	-	-	2 (0.1)	-
Anaphylactic reaction	-	-	2 (0.3)	-	-

### 7.3.3 Adverse Events that Led to Discontinuation of Study Treatment

In the double-blind studies, the proportion of patients who prematurely withdrew from treatment because of an adverse event was higher among patients treated with MTX than patients treated with tocilizumab 8 mg/kg as monotherapy (15 patients, 5.3% vs 11 patients, 3.8%). All adverse events leading to withdrawal in the tocilizumab 8 mg/kg monotherapy group were single occurrences and included events of neutrophil count decrease, ALT increase, pneumonia, and GI perforation.

When tocilizumab was given in combination with DMARDs in the double-blind studies, the proportion of patients who withdrew for adverse events was higher in the tocilizumab 8 mg/kg + DMARD (4.7%) and tocilizumab 4 mg/kg + MTX (4.9%) groups compared with the placebo + DMARD group (2.4%). More patients in both tocilizumab combination groups withdrew compared with the placebo group for adverse events of liver function test abnormalities, increases in bilirubin, hypersensitivity reactions, leukopenia, and neutropenia. More patients in the tocilizumab 8 mg/kg + DMARD group (0.7%) withdrew for GI adverse events than patients in the tocilizumab 4 mg/kg + MTX (0.1%) or placebo + DMARD group (< 0.1%).

#### **7.4 Safety Profile of Tocilizumab – Total Safety Exposure Group**

The overall long-term safety profile of tocilizumab in the Total Safety Exposure group is provided in [Table 29](#). The Total Safety Exposure group includes all patients treated with at least one dose of either 4 mg/kg or 8 mg/kg of tocilizumab. This group also includes patients who escaped to the 4 mg/kg dose, but were then treated with 8 mg/kg after entering the long-term extension studies and patients who reduced their dose from 8 mg/kg to 4 mg/kg for safety reasons. All adverse events are recorded according to the dose administered before the event. The “All TCZ” group includes all patients who received at least one dose of tocilizumab.

This large cumulative data provides an opportunity to calculate rates for rare events and events of special interest. These analyses are provided in the following sections.

**Table 29            Rates of Adverse Events – Total Safety Exposure Group**

	<b>TCZ 4 mg/kg + DMARD N = 1181</b>	<b>TCZ 8 mg/kg + DMARD N = 3242</b>	<b>Control N = 1555</b>	<b>All TCZ N = 3778</b>	<b>Chugai N = 945</b>
Number of adverse events	1993	14380	2703	16397	9500
Adverse events per 100 patient-years	458.30	387.95	395.86	394.38	478.85
Number of serious adverse events	74	568	100	642	541
Serious adverse events per 100 patients years	17.02	15.32	14.65	15.44	26.73
Number of adverse events leading to withdrawal	60	239	49	299	170
Adverse events leading to withdrawal per 100 patient-years	13.80	6.45	7.18	7.19	8.57

## 7.5 Deaths

The frequency of death was comparable in the tocilizumab and placebo groups in the double-blind, controlled studies (Table 30). The rate of death per 100 patient-years was 0.41 (n=5) in the tocilizumab groups and 0.78 (n=5) in the comparator groups.

**Table 30 Listing of Patient Deaths by Trial Treatment and CRTN/Patient Number in Double-Blind Studies (Safety Population)**

Patient Number (Age/Gender)	Cause of Death	Day of Death	Relationship (Investigator Assessment)
<b>TCZ 8 mg/kg</b>			
4013 (46/F)	Cardio-respiratory arrest	150	Unrelated
4221 (76/F)	Gastrointestinal hemorrhage	37	Not known
4929 (50/F)	Myocardial ischemia	40	Unrelated
<b>MTX</b>			
4141 (71/M)	Lung neoplasm malignant	177	Unrelated
<b>TCZ 8 mg/kg + DMARD</b>			
7722 (48/F)	Hemorrhagic stroke	120	Possibly
6713 (75/F)	Post-procedural complication	54	Possibly
<b>Placebo + DMARD</b>			
3298 (46/M)	Coronary artery thrombosis	101	Unrelated
5633 (55/F)	Wegener's granulomatosis	103	Unrelated
7737 (55/F)	Pneumonia	140	Probably
6937 (68/F)	Intestinal obstruction	135	Possibly

A listing of deaths in the open-label, extension studies through October 1, 2007 is provided in Table 31.



**Table 31 Listing of Patient Deaths by Trial Treatment and CRTN/Patient Number in the Open-label, Extension Studies (Safety Population)**

<b>Patient Number (Age/Gender)</b>	<b>Cause of Death</b>	<b>Day of Death</b>	<b>Relationship (Investigator Assessment)</b>
<b>TCZ 8 mg/kg</b>			
3070 (70/F)	Metastatic colon cancer	357	Unrelated
3440 (73/F)	Gastric cancer	534	Remotely
3739 (71/F)	Acute myocardial infarction	183	Unrelated
7328 (72/F)	Bacterial bronchitis	393	Possibly
6554 (63/M)	Completed suicide	47	Unrelated
6981 (58/F)	Septic shock	420	Unrelated
6288 (70/M)	Acute renal failure	441	Unrelated
7366 (45/F)	Completed suicide	477	Unrelated
8888 (75/F)	Pneumonia	268	Possibly
5421 (59/F)	Diverticular perforation	472	Probably
5423 (63/F)	Beta hemolytic streptococcal infection	234	Possibly
5883 (67/M)	Myocardial infarction	341	Unrelated
5326 (68/F)	Progressive idiopathic polyneuropathy	203	Possibly
5151 (83/F)	Unevaluable event	100	Possibly
5687 (57/F)	Myocardial infarction	372	Possibly
4943 (70/F)	Cardiac failure	200	Unrelated

Patient 7575 was reported as having died in the 4MSU in error and thus, is not included in this table.

Deaths occurring in the Chugai program up to January 31, 2008 in RA are listed in [Table 32](#), while those occurring in non-RA indications are listed in [Appendix 18](#). The most common causes of death observed in the RA population are cardiovascular and infection related.

**Table 32 Listing of Deaths in Chugai RA Studies (January 31, 2008)**

Treatment	Study	Age / Gender	Cause of Death	Relationship to Treatment
TCZ 1 mg/kg	LRO300	70F	Myocardial ischemia	No
TCZ 2 mg/kg	LRO301	61M	Lung cancer	No
TCZ 8 mg/kg	MRA009JP	60F	EB virus reactivation, Hodgkin's disease	Yes, Yes
TCZ 8 mg/kg	MRA214JP	52M	Gastric Cancer	Yes
TCZ 8 mg/kg	MRA214JP	81M	Bronchopulmonary aspergillosis	No
			Pulmonary fibrosis	Yes
TCZ 8 mg/kg	MRA225JP	26F	Cardiac failure	No
After October 1, 2007 to January 31, 2008				
TCZ 8 mg/kg	MRA010JP	79M	Pneumonia	Yes
TCZ 8 mg/kg	MRA214JP	62M	Drowning	No

The rate of death per 100 patient-years up to the October 1, 2007 reporting date is 0.57 per 100 patient-years in patients treated with tocilizumab and 0.88 per 100 patient-years in patients treated with placebo or DMARDs ([Table 33](#)).

**Table 33 Number and Rate of Deaths Reported in all Patients Exposed to Tocilizumab**

	TCZ 4 mg/kg + DMARD N = 1181	TCZ 8 mg/kg <sup>a</sup> N = 3242	Control N = 1555	All TCZ N = 3778	Chugai* N = 957
Cardiac and vascular	-	7	2	7	2
Infection	-	5	1	5	2
Gastrointestinal	-	2	1	2	-
Malignancy	-	2	1	2	2
Cardiac Failure	-	-	-	-	-
Suicide	-	2	-	2	-
Wegener's Granulomatosis	-	-	1	-	-
Polyneuropathy	-	1	-	1	-
Unknown	-	1	-	1	-
Renal Failure	-	1	-	1	-
Total	-	21	6	21	6
Deaths per 100 patient-years of exposure	-	0.57	0.96	0.51	0.30

<sup>a</sup>includes monotherapy

\*RA only; includes 12 patients from MRA225JP

## **7.6 Adverse Events of Special Interest**

The following sections discuss adverse events of interest. These events are highlighted because they are adverse events associated with RA, are known to be associated with other treatments for RA, and/or were seen in the tocilizumab clinical development program.

### **7.6.1 Infections**

Patients with RA are at a higher risk of infection than the general population mainly because of altered immunological functions and other factors including therapies used to treat the underlying disease (eg, corticosteroids, immunomodulating agents). Tocilizumab, similar to other biologic DMARDs, appears to increase the potential for the development of certain types of infection.

In the double-blind studies, the overall incidence of infections was lower in the tocilizumab 8 mg/kg monotherapy group than in the MTX group, and higher in the tocilizumab 8 mg/kg and 4 mg/kg combination therapy groups than in the respective DMARD control group ([Table 34](#)). The most common infections reported in the double-blind controlled studies were upper respiratory infection, bronchitis, and urinary tract infection.

The rate of serious infections in the double-blind studies was highest in the tocilizumab 8 mg/kg + DMARD group ([Table 34](#)). This rate of 5.18 events per 100 patient-years is consistent with the rates recorded for other biologic treatments for RA (5.32 per 100 patient-years [28]) and the nature of serious infections observed with tocilizumab was similar to that reported with other biologics used in the treatment of RA. The most common serious infections were pneumonia, cellulitis, diverticulitis, urinary tract infection, gastroenteritis, and sepsis ([Table 35](#)).

**Table 34 Overview of Infections – Double-Blind Studies**

	<b>TCZ 8 mg/kg N = 288</b>	<b>MTX N = 284</b>	<b>TCZ 4 mg/kg + DMARD N = 774</b>	<b>TCZ 8 mg/kg + DMARD N = 1582</b>	<b>Placebo + DMARD N = 1170</b>
Patients with at least one infection	99 (34.4%)	106 (37.3%)	270 (34.9%)	592 (37.4%)	374 (32%)
Rate of infections per 100 patient-years of exposure	106.49	109.24	121.54	117.85	103.5
Patient withdrawal due to infection	1 (0.3%)	1 (0.4%)	5 (0.6%)	8 (0.5%)	7 (0.6%)
Patients with at least 1 serious infection	4 (1.4%)	2 (0.7%)	13 (1.7%)	38 (2.4%)	17 (1.5%)
Rate of serious infections per 100 patient-years of exposure	2.86	1.50	4.35	5.18	3.75

**Table 35 Summary of Serious Infections Reported by at Least One Patient Treated with Tocilizumab – Double-blind Studies**

	TCZ 8 mg/kg N = 288	MTX N = 284	TCZ 4 mg/kg + DMARD N = 774	TCZ 8 mg/kg + DMARD N = 1582	Placebo + DMARD N = 1170
<b>Preferred term</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Pneumonia	2 (1)	1 (<1)	6 (1)	9 (1)	4 (<1)
Cellulitis	-	-	-	10 (1)	1 (<1)
Herpes Zoster	-	-	-	5 (<1)	-
Sepsis	-	1 (<1)	2 (<1)	1 (<1)	1 (<1)
Bronchitis	-	-	1 (<1)	1 (<1)	1 (<1)
Gastroenteritis	-	-	3 (<1)	-	-
Urinary tract infection	-	-	1 (<1)	1 (<1)	4 (<1)
Total	4 (1)	2 (1)	13 (2)	38 (2)	17 (2)

Few infections led to withdrawal (< 1%) and similar proportions of patients withdrew because of infections in each tocilizumab treatment group. Most patients with a serious infection temporarily interrupted dosing.

Prolonged exposure to tocilizumab 8 mg/kg was not associated with an increase in the rate of serious infections above that seen in the controlled 24-week studies (4.45 per 100 patient-years) ([Table 36](#)).

**Table 36 Rate of Serious Infections – Total Safety Exposure**

	TCZ 4 mg/kg + MTX N = 1181	TCZ 8 mg/kg N = 3242	Control N = 1555	All TCZ N = 3778	Chugai N = 945
Rate of serious infections per 100 patient-years of exposure	4.6	4.45	3.66	4.45	6.27
Rate of deaths due to infections per 100 patient-years of exposure	-	0.13	0.16	0.12	NA

NA=not available

Considering the Total Safety Exposure group, five patients treated with tocilizumab and one patient in the control group were reported by the investigator to have died of an infection. The types of infection that led to death included pneumonia (one patient in the tocilizumab 8 mg/kg group and one patient in the control group), sepsis (three patients in the tocilizumab group), and bacterial bronchitis.

Opportunistic infections were reported following ongoing exposure to tocilizumab. Since these events are infrequent, they are provided as incidences rather than rates for the Total Safety Exposure group in [Table 37](#).

**Table 37**                      **Number (Rate per 100 Patient-Years) of Opportunistic Infections – Total Safety Exposure**

	TCZ 4 mg/kg + DMARD N = 1181	TCZ 8 mg/kg <sup>a</sup> N = 3242	Control N = 1555	All TCZ N = 3778	Chugai N = 945
<i>Myobacterium avium-intracellulare/ Myobacterium avium complex</i>	-	1 (0.03)	-	1 (0.02)	-
Tuberculosis	-	2 (0.05)	-	2 (0.05)	3 (0.15)
<i>Pneumocystis carinii</i> pneumonia	1 (0.23)	-	-	1 (0.02)	1 (0.05)
Epstein-Barr reactivation	-	-	-	-	1 (0.05)
Pulmonary aspergillosis	-	-	-	-	1 (0.05)
Candida osteomyelitis*	-	1 (0.03)	-	1 (0.02)	-
Herpes zoster (serious)*	-	8 (0.22)	-	8 (0.19)	13 (0.64)
Total	1 (0.23)	12 (0.32)	-	13 (0.31)	19 (0.95)

<sup>a</sup>Includes monotherapy

\*Post October 1, 2007

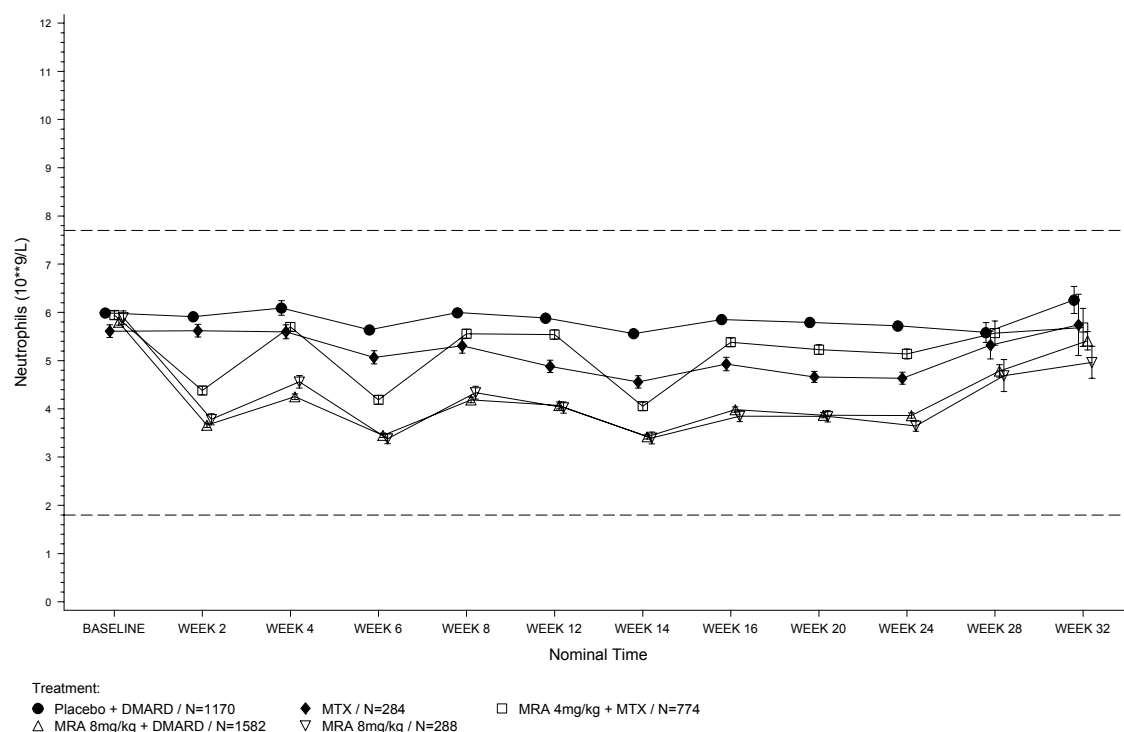
\*\*One case of ophthalmic; all other cases were cutaneous cases.

### **7.6.1.1    Neutrophil Counts**

Circulating neutrophil counts are increased in RA patients relative to the general population. Given the mechanism of action of tocilizumab, a reduction in circulating neutrophil count was expected. Patients were required to have a neutrophil count  $\geq 2000/\text{mm}^3$  to enter the double-blind studies. Concentration-dependent variability in mean circulating neutrophil counts was observed in all of the tocilizumab treatment groups. In the tocilizumab 4 mg/kg group, the circulating neutrophil count tended to return towards baseline levels as tocilizumab concentration declined during the latter half of the monthly interdose period. Mean counts remained within the normal range throughout the 24-week treatment period (Figure 19). The percentage of patients with grade 3 or 4 neutropenia is summarized in Table 38.

**Figure 19 Absolute Neutrophil Counts (Mean  $\pm$  SEM) Over Time - Double-blind Studies (Safety Population)**

Mean Plot of Neutrophils ( $10^9/L$ ) over Time - Absolute - 6 Month Pooled Data (Safety Population)



Only Worst values within a time window per patient are summarized. Local Analysis is excluded where Central analysis is available on the same day. Escape data is excluded. Dashed horizontal lines represent upper and lower limits of project-specific or standard COG3007 reference ranges. sgbs2\_ab\_neutr 21SEP2007 16:57 Project: cd11935h Protocol: hls\_pool

**Table 38 Summary of Grade 3 and Grade 4 Neutropenia – Double-blind Studies (Safety Population)**

	TCZ 8 mg N = 288	MTX N = 284	TCZ 4 mg/kg + MTX N = 774	TCZ 8 mg/kg + DMARD N = 1582	Placebo + DMARD N = 1170
Grade 1 (1500-LLN/mm <sup>3</sup> )	51 (18%)	22 (8%)	88 (11%)	298 (19%)	30 (3%)
Grade 2 (1000-1500/mm <sup>3</sup> )	30 (10%)	6 (2%)	53 (7%)	179 (11%)	10 (< 1%)
Grade 3 (500-1000/mm <sup>3</sup> )	9 (3%)	1 (< 1%)	9 (1%)	48 (3%)	-
Grade 4 (< 500/mm <sup>3</sup> )	-	-	3 (< 1%)	5 (< 1%)	-

LLN = lower limit of normal

During the studies, investigators were instructed to discontinue treatment if the neutrophil count fell below 500/mm<sup>3</sup>. As required by the protocol, all 12 patients (8 patients in the double-blind studies and 4 patients in the Total Safety Exposure group) with a neutrophil count < 500/mm<sup>3</sup> were withdrawn and their levels returned to baseline within 4 to 8 weeks (where follow-up information is available). These were the only patients who

discontinued treatment because of neutropenia. There were an additional three patients treated with tocilizumab and one patient treated with MTX who interrupted treatment because of a decrease in neutrophil count that did not reach this level.

In the double-blind studies, five infections (<1%) occurred in patients with neutrophil counts between 500 and < 1000/mm<sup>3</sup> 1 month prior to the infection (two bronchitis, one sinusitis, one pharyngitis, and one conjunctivitis). One event (conjunctivitis) occurred in a patient receiving tocilizumab 4 mg/kg + MTX and four events occurred in patients receiving tocilizumab 8 mg/kg + DMARD. There were no infection adverse events in the double-blind studies that occurred in patients with neutrophil counts < 500/mm<sup>3</sup> in the double-blind studies.

In the Total Safety Exposure group, there was no increase in the frequency of grade 3 or 4 neutropenia with increased duration of exposure to tocilizumab. Tocilizumab-related grade 4 neutropenia was reported by 12 patients out of a total of 3778 exposed to tocilizumab in the Total Safety Exposure group. All twelve of these patients discontinued treatment.

Treating physicians should be alert to the signs of infection and manage all cases aggressively. Tocilizumab treatment should not be initiated in patients with an active infection. Patients should undergo a tuberculosis screen before starting treatment and if positive, initiate tuberculosis treatment according to ACR guidelines. Live attenuated vaccines should not be given concurrently with tocilizumab.

### **7.6.2 GI Perforation**

GI symptoms and events are common among patients with RA as most take NSAIDs for the relief of pain and many may take low-dose aspirin to prevent cardiovascular events. Upper GI symptoms such as dyspepsia are the most common side-effects that occur with NSAID use. In addition, the risk of serious upper GI clinical events such as bleeding ulcers and perforation is increased by about two to five times compared with patients not taking these treatments [29]. Not only is NSAID use known to cause damage to the gastroduodenal mucosa, but more recently, NSAID and corticosteroid use have been associated with lower GI pathology including complicated diverticular disease and perforation [30, 31]. A retrospective study in a large population of RA patients (n=1666) in Finland found that NSAID-induced perforation or bleeding from the lower GI accounted for 36% of NSAID-attributable deaths [32]. A further examination of the same cohort found 12 deaths associated with diverticular disease. The authors concluded that complicated diverticular disease is a more important cause of death in patients with RA than is generally recognized.

The potential effects of tocilizumab on GI mucosa and motility were investigated in the preclinical program. Tocilizumab exposure was not associated with adverse effects on GI mucosal integrity or motility in pre-clinical testing.



### 7.6.2.1 GI Perforation in the Tocilizumab RA Program

Three patients in the 6-month, double-blind studies had evidence of a GI perforation during the 6-month trial program (Table 39).

**Table 39**      **Number (%) and Rate of GI Perforation Events in the Double-blind Controlled Studies**

	<b>TCZ 8 mg/kg N = 288 125.6PY</b>	<b>MTX N = 284 122.9PY</b>	<b>TCZ 4 mg/kg + DMARD N = 774 320.9PY</b>	<b>TCZ 8 mg/kg + DMARD N = 1582 684.7PY</b>	<b>Placebo + DMARD N = 1170 461.8PY</b>
Preferred term	%	%	%	%	%
Diverticular perforation	0	0	0	1	0
Gastrointestinal perforation (duodenal)	1 (0.3%)	0	0	0	0
Large intestine perforation	0	0	0	1	0
Total	1 (0.3%)	0	0	2 (0.13%)	0
Rate per 1000 patient-years	7.9			2.92	

Two of these events occurred following endoscopy. Details for these patients are as follows:

- A 76-year-old female receiving treatment with tocilizumab 8 mg/kg monotherapy was admitted with GI bleeding from a duodenal ulcer which was managed conservatively. She underwent three endoscopy evaluations for persistent bleeding and the ulcer perforated after the third. This patient arrested and died during an X-ray examination.
- A 65-year-old male patient receiving treatment with tocilizumab 8 mg/kg and MTX initially presented with a pelvic abscess which was successfully managed conservatively. He later underwent a diagnostic colonoscopy which was followed by a large intestine perforation.
- An 82-year-old female with a past medical history of diverticular disease who experienced abrupt abdominal pain found to be due to a diverticular perforation 5 days after her second dose of tocilizumab 8mg/kg; she recovered after surgery for this event.

To March 31, 2008, a total of eight patients in the extension program and 2 patients in the 12-month radiographic study, WA17823, have reported a GI perforation. Of the 8 cases in the extension program, five were complicated diverticulitis, one was due to ischemic bowel necrosis, one patient had a colovaginal fistula, and one patient had an esophageal perforation following intubation during general anesthesia for a knee replacement. Of the 2 cases in WA17823, one patient (0.25%) received tocilizumab 4 mg/kg (diverticular perforation) while one (0.25%) received tocilizumab 8 mg/kg and had a jejunal perforation suspected after a CT scan to investigate the cause of acute abdominal pain; however, the perforation was not confirmed at laparoscopy.

Two patients died: a patient with a perforated sigmoid diverticulum and the patient with an esophageal perforation. The patient with a perforated sigmoid diverticulum had an extremely complicated post-operative course requiring repeated surgical treatments for

anastomotic breakdowns due to bowel ischemia and died 8 months after the index event of overwhelming sepsis. The patient who had an esophageal perforation after intubation for another procedure died of complications of this iatrogenic event.

Thus, to date, a total of three patients have died secondary to GI perforations or their complications.

Additionally, there were six patients, all receiving tocilizumab 8 mg/kg, that reported an intra-abdominal abscess. Three were diverticular abscesses, one a tubo-ovarian abscess, one a necrotizing appendicitis, and one an abscess of the gall bladder in a patient with gallstones.

GI perforations were also reported by several patients participating in Chugai studies: 6 in adult RA patients and one in a patient in a compassionate release program. One of these was a perforated esophagus which followed an esophageal biopsy taken at endoscopy for epigastric pain. Two others were perforations in the duodenum and four were lower bowel perforations.

The only case of bowel perforation reported in a patient receiving placebo treatment was a bowel perforation as a result of a leaking anastomosis following surgery for colonic cancer.

#### **7.6.2.2 GI Perforations Reported in Other Indications**

In addition to investigations in RA, tocilizumab is approved in Japan as a treatment for Castleman's Disease. One 56-year-old male patient with Castleman's disease received 160 doses of tocilizumab as well as treatment with prednisolone. He had a medical history of gastric ulcer and was taking teprenone for gastric mucosal protection. Prednisone was discontinued when his Castleman's Disease was controlled. One month prior to the event, prednisone was re-started following which he developed abdominal pain and peritonitis. At laparotomy, a perforation of the stomach was repaired. This patient recovered and is continuing tocilizumab therapy for his Castleman's Disease.

A 24-year-old, Japanese patient receiving tocilizumab therapy for Crohn's disease underwent colonoscopy because of GI hemorrhage. The hemorrhage was diagnosed as being due to colonic ulceration. The day following the colonoscopy, a CT demonstrated free intra-abdominal air. A laparotomy was performed, but no perforation was found. Finally, a 10-year-old Japanese male with sJIA of 6 years duration received 23 doses of tocilizumab (various strengths) and other medications including multiple steroids and NSAIDs. His medical history included gastric ulceration and GI hemorrhage. He was taking famotidine for gastric mucosal protection. Treatment with famotidine was discontinued and approximately 1 month later, the patient had intermittent epigastric pain and was anemic (Hb 8.7 g/dL). He was treated with rebamipide and famotidine and then lansoprazole for about 5 weeks when the pain went away. Nine days later the patient was hospitalized with hypovolemic shock and acute abdomen. Laparotomy showed duodenal perforation. The event resolved after a complicated course.

### 7.6.2.3 Overall Incidence of GI Perforation

The overall incidence of GI perforation reported in all tocilizumab-treated RA patients through March 31, 2008 is displayed in [Table 40](#).

**Table 40**      **Number (%) and Rate (per 1000 patient-years) of GI Perforations in the Tocilizumab RA Indication (through March 31, 2008)**

Site	Roche Phase III RA Program			All TCZ	Chugai
	MTX/DMARD N=1555 682.82PY	TCZ 4mg/kg + DMARD N=774 523.72PY	TCZ 8mg/kg +/- DMARD N=3251 6101PY	TCZ +/- DMARD N=4025 6624.72PY	TCZ 8mg/kg N=945 2830 PY
<b>Upper GI</b>					
Number (%)	0	0	3 (0.09%)	3 (0.07%)	3 (0.32%)
Rate (per 1000 PY)	0	0	0.49	0.45	1.34
<b>Lower GI</b>					
Number (%)	0	1 (0.13%)	9 (0.28%)	10 (0.25%)	4 (0.42%)
Rate (per 1000 PY)	0	1.90	1.48	1.51	1.79

### 7.6.2.4 Epidemiology of Gastrointestinal Perforation in RA

#### Upper GI

Upper GI perforation occurred in 3 of 4047 recipients of rofecoxib (1.1/1000 patient-years) and 4 of 4029 recipients of naproxen (1.5/ 1000 patient-years) in a large study investigating GI toxicity in RA patients [34]. As NSAIDs are widely used in patients with RA, NSAIDs are a potential confounder for associations found between other therapies and the occurrence of upper GI perforation.

#### Lower GI/Diverticular Perforation

As noted above, lower GI complications may be encountered in patients receiving NSAIDs and corticosteroid therapy for RA. In a case-control study Mpofu et al showed an association between perforation of diverticular abscess and rheumatic diagnoses compared to the general population (Odds Ratio 3.5) [31]. Precise incidence figures for RA populations are not available in the literature. Roche has performed studies to investigate the incidence of GI perforations in RA patients from the United Healthcare database. The estimated incidence of lower GI perforation provides a reference range for the perforations in the tocilizumab program. The estimates derived are provided in [Table 41](#).

**Table 41 GI Perforation Rate (per 1000 Patient-Years) in RA Patients in the United Health Care Database**

	Rate/1000 PYs	95% CI
Exposed to anti-TNF*	1.32	0.77, 1.87
Exposed to methotrexate*	1.14	0.76, 1.52
Exposed to corticosteroid*	3.91	3.05, 4.76

\*Current exposure, or stopped exposure within last 12 months

The lower GI perforations reported were largely related to complications of diverticulitis in patients also receiving corticosteroids. Given the range of estimates for the incidence of lower GI perforations in RA patients based on the epidemiological studies conducted by Roche, the number of cases of lower GI perforation expected in the tocilizumab 8 mg/kg group, 4 mg/kg group, and control population was 7 to 23 (12 observed), 0 to 2 (1 observed), and 0 to 3 (none observed), respectively.

As for patients receiving treatment with NSAIDs and corticosteroids, provision of agents which increase gastric mucosal protection would be appropriate for patients being treated with tocilizumab. Caution is advisable in patients with a history of complicated diverticular disease, as these individuals may be at higher risk of recurrence of these complications. Patients receiving tocilizumab treatment who experience a change in bowel habit, severe abdominal pain, or GI bleeding should be promptly investigated with early referral for surgical consultation as clinically indicated.

### 7.6.3 Malignancy

Growth of an existing cancer is a known risk of immunosuppressive therapy in RA patients. In the 6-month, double-blind studies, malignant neoplasms were detected in 15 of 2644 tocilizumab-treated patients and in 8 of 1454 placebo treated patients for comparable rates of 1.33 events per 100 patient-years and 1.27, respectively. Following longer-term treatment, the rate in the Total Safety Exposure group was 1.45 events per 100 patient-years; excluding non-melanoma skin cancers, the rate was 0.91/100 patient-years.

The cases reported in tocilizumab-treated patients occurred in seven different organ systems (skin, respiratory tract, breast, gastro-intestinal, reproductive system, liver, renal, and urinary tract). With the exception of four hematological malignancies (two non-Hodgkin's lymphomas, one gammopathy with signs of pre-existence, and one Hodgkin's lymphoma with pre-existing disease), the reported malignant neoplasms were all solid tumors, that varied in cell type and location. Thirty-seven percent and 62% of reported malignancies were reported within 6 to 12 months of initiating tocilizumab therapy.

Considering the Total Safety Exposure group (Table 42), six of the 19 patients with non-melanoma skin cancers had a previous history of a non-melanoma skin cancer or actinic keratosis. Of the two patients with prostate cancer, one had a prior history of prostatic hyperplasia.

**Table 42 Summary of the Malignancy Reports from the Overall Roche and Chugai RA Trials**

	TCZ 4 mg/kg + DMARD PY=435 n (rate/100 PY)	TCZ 8 mg/kg +/- DMARD PY=3707 n (rate/100 PY)	Placebo PY=628 n (rate/100 PY)	ALL TCZ PY=4142 n (rate/100 PY)	Chugai (N=957) PY=2009 n (rate/100 PY)
Total	5 (1.15)	55 (1.48)	8 (1.27)	60 (1.45)	18 (0.90)
Solid					
Lung	2 (0.46)	10 (0.27)	1 (0.16)	12 (0.29)	2 (0.10)
Breast	0	4 (0.11)	1 (0.16)	4 (0.10)	4 (0.20)
Cervix	1 (0.31)	3 (0.08)	0	4 (0.10)	1 (0.05)
Colo-Rectal	0	3 (0.08)	2 (0.30)	3 (0.07)	4 (0.20)
Gastric	0	3 (0.08)	0	3 (0.07)	1 (0.05)
Prostate	0	2 (0.05)	1 (0.16)	2 (0.05)	0
Endometrial/ Uterine	0	2 (0.05)	0	2 (0.05)	0
Thyroid	0	2 (0.05)	0	2 (0.05)	0
Metastatic (primary unknown)	0	2 (0.05)	0	2 (0.05)	0
Gall bladder	0	0	0	0	1 (0.05)
Bladder	0	0	0	0	2 (0.10)
Pancreatic cancer	0	0	0	0	1 (0.05)
Ovarian	0	1 (0.03)	0	1 (0.02)	0
Glioblastoma	0	1 (0.03)	0	1 (0.02)	0
Non-melanoma Skin cancer	2 (0.46)	4 (0.11)	2* (0.32)	22 (0.53)	NA
Hematologic Gammopathy	0	1 (0.03)	0	1 (0.02)	0
Lymphoma	0	1 (0.03)	1 (0.16)	1 (0.02)	2 (0.10)

\*One patient reported two skin malignancies.

In order to determine if there is indirect evidence for increased tumor growth on tocilizumab, the malignancy rates in confirmed cases from the US were compared to Surveillance Epidemiology and End-Results (SEER) data, which come from a US, general-population-based cancer registry program (Table 43). The SEER comparison for US-confirmed malignancies showed a SIR of  $\geq 2$  for colorectal and uterine cancer and a SIR of 1.6 for lung carcinoma.

**Table 43 SEER Comparison of Confirmed Cases of Malignancy – SIR for US Patients Only (N=1173)**

Organ Class	SIR	95% CI	
		Low	High
All Sites	0.866	0.816	0.918
Colon and Rectum	2.001	1.720	2.329
Corpus Uteri	2.205	1.707	2.848
Female Breast	0.402	0.237	0.681
Lung	1.649	1.485	1.831
Prostate	0.675	0.344	1.326

### Interpretation of the SEER data: Malignancy Rates in the RA Population

The occurrence of cancer in the RA population has been well-studied. Of the sites in the Roche studies where the relative risk is currently elevated, the incidence in lung cancers and lymphomas has been documented to be higher in RA patients compared with the general population. A recent meta-analysis reported a 1.5- to 3.5-fold increase in the incidence of lung cancer with the effect estimate (SIR) generated by this random effects analysis to be 1.63 (95% CI 1.43-1.87) [35].

Lymphoma is widely accepted to occur more frequently among RA patients than in the general population. The increased risk (regardless of lymphoma type) generated a SIR of 2.08 (95% CI, 1.80-2.39) in a recent meta-analysis using a random effects model [35]. The analysis found a higher risk for Hodgkin's lymphoma than for non-Hodgkin's lymphoma, estimating SIRs of 3.29 (95% CI, 2.56-4.22) and 1.95 (95% CI, 1.70-2.24), respectively.

In summary, when comparing the confirmed US malignancy cases with SEER, an increased malignancy SIR was seen for uterine, colorectal, and lung cancers. The numbers for these malignancies are small and therefore, it is inappropriate to draw conclusions until greater exposure on tocilizumab accrues. The data from the tocilizumab studies conducted to date, therefore, are not yet sufficient to determine if a link exists between tocilizumab and the development of any type of cancer. Continued surveillance of patients on tocilizumab will be required. Roche will be monitoring all reports of malignancy closely through its risk assessment and management plan.

Roche proposes to collect additional information on malignancies as part of its risk assessment and management plan for tocilizumab (Section 8).

### **7.6.4 Demyelinating Disorders**

Cases of new onset or exacerbation of central nervous system demyelinating disorders have been reported in association with marketed biological treatments for RA, mostly with TNF antagonists [36, 37]. In the clinical development program for tocilizumab in RA, three cases with white matter changes on MRI were observed (patient summaries provided below). In addition, there were three patients with other neurological events of interest including one patient with optic neuritis, one patient with progressive chronic idiopathic polyradiculoneuropathy, and one patient with cranial neuropathy. The patient with polyradiculoneuropathy died and the other two patients continued on therapy.

#### Patients with MRI findings:

- Patient 5689: 64-year-old male, RA for 7 years, 8 mg/kg tocilizumab. Prior immunosuppressives: gold, MTX, hydroxychloroquine, leflunomide, etanercept, infliximab, adalimumab, anakinra, and sulfasalazine. History: chronic migraine, headache, and tremor. On study day 253, an MRI showed white matter lesions consistent with demyelination. The patient withdrew from the study.
- Patient 114002: 72-year-old, Japanese female, 8 mg/kg tocilizumab. History: type 2 diabetes, hypertension, hyperlipidemia, aortic stenosis, peripheral edema, cervical subluxation, and ticlopidine for prophylaxis of thrombosis. After 3 years of tocilizumab therapy, she was noted to have deteriorating mental status; an MRI

- revealed extensive white matter lesions in both cerebral cortices and atrophy of the cerebellum; drug-induced leukoencephalopathy could not be excluded.
- Patient 1401: 56-year-old female, RA of 5 years, 4 and 8 mg/kg tocilizumab. History: headaches. Prior immunosuppressive: MTX. On study day 799, after syncope, an MRI showed multifocal paraventricular white matter lesions suggestive, but not definitive for, demyelinating disease. Tocilizumab treatment was permanently discontinued 4 months later.

The mechanism leading to the observed neurological symptoms is not fully understood. While tocilizumab cannot be excluded as a cause, underlying vascular disease, coagulopathy, or long-term treatment with immunosuppressive therapy may cause or contribute to the conditions described. Treating physicians should be alert for the development of new neurological symptoms or progression of existing neurological conditions and apply appropriate diagnostic procedures and treatment.

Roche proposes to collect additional information on demyelinating disorders as part of the risk assessment and management plan for tocilizumab (Section 8).

### **7.6.5 Hypertensive, Cardiovascular, and Stroke Adverse Events**

Serious cardiovascular disorders occur at a higher rate in RA patients than in age- and gender-matched individuals without RA, substantially contributing to premature mortality and morbidity for these patients [38, 39, 40]. Because of this increased risk in the RA patient population, cardiovascular and hypertension adverse events are discussed in more detail in this section.

#### **7.6.5.1 Hypertension-Reported Adverse Events**

Hypertension is a modifiable cardiovascular risk factor in patients with RA. In patients with RA, hypertension may be induced by physical inactivity, systemic inflammation, and medications such as NSAIDs/Cox-2 inhibitors, corticosteroids, cyclosporine, and leflunomide. Conventional antihypertensive treatment appears to be effective in patients with RA.

The incidence of diagnosed hypertension reported at baseline was similar across treatment groups (28.5% to 35%). In the double-blind studies, hypertension or increases in blood pressure were reported as an adverse event in 5.2% of the patients in the tocilizumab 4 mg/kg + MTX group, 5.1% in the tocilizumab 8 mg/kg + DMARD group, 6.3% in the tocilizumab 8 mg/kg group, 3.1% in the DMARD control group for the combination therapy studies, and 2.8% in the MTX group of the monotherapy study. Over 90% percent of hypertension adverse events were regarded as mild or moderate in intensity. None of these patients withdrew. In these studies, 48% to 89% of patients were taking NSAIDs and approximately 60% were taking corticosteroids. From the double-blind studies, approximately half of the hypertension adverse events were reported in patients with pre-existing hypertension and approximately one third of the hypertension adverse events occurred during or within 24 hours of an infusion. Treatment with conventional antihypertensive therapy was effective in reducing blood pressure in the patients in whom antihypertensive treatment was indicated.



Mean systolic and diastolic blood pressure did not change in the various treatment groups during the double-blind studies. Categorical analysis of preinfusion blood pressure measurements according to the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure showed that there was no increase in the proportion of patients with Stage 1 or Stage 2 hypertension between baseline and 16 weeks, before the last infusion of tocilizumab in the double-blind period.

While there was an increase in investigator reported hypertension adverse events in tocilizumab-treated patients compared to controls, there was no increase in mean blood pressure and the events were treatable with standard therapies.

#### **7.6.5.2 Cardiovascular Events**

In the 24-week, double-blind, controlled studies, the overall incidence of all cardiac adverse events was similar in the tocilizumab and placebo treatment groups. Most events were rated by the investigators as mild to moderate in intensity.

The number of patients experiencing any serious cardiac, nervous system, or vascular adverse event in the double-blind trials was small and similar across treatment groups. Serious cardiac disorders were reported in 0.4% of tocilizumab-treated and control-treated patients. There were five patients who had either a stroke or an intracranial hemorrhage in the tocilizumab-treated groups and one in the placebo + DMARD group. These patients had risk factors for cerebral events such as congenital vascular abnormality, diabetes, hyperlipidemia, atherosclerosis, or a coagulopathy.

An additional three patients experienced serious cardiac events (myocardial infarction, cardio-respiratory arrest, and stroke) while receiving MTX in the transition phase of the monotherapy study, WA17824. As the transition phase for this study continued beyond the 24-week treatment period (see Section 6.6), these events are not included in the data from the pooled double-blind studies.

The current long-term database includes 3778 patients, with 2121 treated for at least 1 year and represents a total of 4142 patient-years of exposure. All serious adverse events related to atherosclerosis were analyzed separately to establish the incidence of the events in 6-month periods beginning with the double-blind period through the open-label extension period. The incidences of these atherosclerotic events, myocardial infarction, and stroke did not increase over time. The overall incidences of myocardial infarction (0.36 events per 100 patient-years) and stroke (0.22 events per 100 patient-years) are consistent with those reported in epidemiology and registry studies [41, 42, 43, 44, 45].

In summary, patients treated with tocilizumab experienced cardiovascular adverse events similar to controls and the incidence of myocardial infarction and stroke were within the range expected on the basis of historical data.

#### **7.6.5.3 Lipid Parameters**

Serum lipids, total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides increased in patients in both the tocilizumab monotherapy and



4 mg/kg or 8 mg/kg combination therapy groups more than in patients in the placebo and MTX groups ([Table 44](#)).

**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.

In the double-blind studies, serum LDL increased from < 130 mg/dL at baseline to ≥ 130 mg/dL at the last observation in 11.3% of patients in the MTX group, 22.6% of patients in the tocilizumab 8 mg/kg group, 8.8% of patients treated with DMARDs, 15.4% of patients treated with 4 mg/kg tocilizumab + DMARD, and 21.8% of patients treated with 8 mg/kg tocilizumab + DMARD. Serum LDL increased from < 160 mg/dL to above 160 mg/dL in 6.7% of patients in the MTX group, 17.4% of patients on tocilizumab 8 mg/kg, 3.5% of patients treated with DMARDs, 11.0% of those treated with 4 mg tocilizumab + DMARD, and 13.2% of those treated with 8 mg tocilizumab + DMARD.

Lipid increases occurred as early as 6 weeks after initiation of tocilizumab treatment and remained stable through treatment in the open-label extension studies.

There was a slight increase in the LDL/HDL and the ApoB/ApoA1 ratios in the tocilizumab treatment groups ([Table 45](#)).

**Table 45 Atherogenic Indices for Double-blind Study Population**

	TCZ 8 mg/kg n=260	MTX n=253	TCZ 8 mg/kg + DMARD n=1467	TCZ 4 mg/kg + DMARD n=714	Placebo + DMARD n=1068
<b>LDL/HDL Ratio</b>					
Baseline	2.18	2.25	2.16	2.11	2.14
Week 14	2.48	2.23	2.35	2.33	2.13
<b>ApoB/ApoA1</b>					
Baseline	0.77	0.78	0.74	0.73	0.74
Week 14	0.79	0.74	0.75	0.74	0.73

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.

In the double-blind studies, mean LDL values increased by 11.7 mg/dL in tocilizumab-treated patients who were also receiving statins compared to 18.7 mg/dL in tocilizumab-treated patients not receiving statins. In patients receiving tocilizumab in the extension studies who initiated statin therapy, mean LDL values decreased by 24% and total cholesterol by 18.2%, whereas mean HDL increased by 2.1% in response to treatment.

Tocilizumab does not elevate serum lipids in healthy volunteers or animals. This suggests that lipid elevations seen with tocilizumab in RA patients may be related to control of inflammation. The elevations in LDL correlated moderately with decreases in CRP in all treatment arms,  $r=-0.2$  to  $0.41$ , ( $p<0.001$ ) as well as with SAA and haptoglobin. Several studies also report increases in LDL and HDL following suppression of systemic inflammation in response to treatment of RA with TNF $\alpha$  inhibitors [46, 47].

In summary, tocilizumab raises LDL, HDL, total cholesterol, and triglycerides within 6 weeks of initiating treatment. Similar lipid elevations have been observed following treatment with anti-TNF biologics. Serum lipids decreased in patients taking tocilizumab who initiated statin therapy. Modifiable cardiovascular risk factors (eg, LDL and blood pressure) should be routinely monitored and appropriate therapy initiated.

### 7.6.6 Liver Enzyme Elevations

Liver enzyme elevations have been described with MTX, leflunomide, and other treatments for RA. Patients with ALT and AST  $>1.5\times$  ULN at screening were not eligible to enter the tocilizumab trials and patients with significant hepatic disease, hepatitis B or C, or active hepatitis were excluded from the tocilizumab trials.

For all double-blind studies in which tocilizumab was administered with a DMARD, patients were to have been on a stable dose of DMARD (WA18063), or specifically MTX (studies WA18062, WA17822, and WA17823) for at least 8 weeks prior to baseline.

All protocols included specific guidance for the management of liver enzyme elevations. When ALT or AST elevations  $\geq 3\times$  ULN were noted, the next scheduled dose of tocilizumab was to be withheld, values remeasured every 2 weeks thereafter, and the dose was to be resumed at the next scheduled 4-weekly visit after ALT and AST values

returned to a value less than 3x ULN. When ALT or AST were  $> 2x$  ULN and less than  $< 3x$  ULN, blood samples were to be obtained immediately prior to the next dose of tocilizumab to verify that the ALT or AST value remained  $< 3x$  ULN prior to treatment.

Patients were to be discontinued if: 1) there was a second ALT or AST  $\geq 3x$  ULN following the held dose and prior to recommencement of treatment, 2) the ALT or AST was  $> 5x$  ULN at any time, 3) any two consecutive doses of tocilizumab were missed due to ALT or AST elevations, or 4) indirect bilirubin was  $> 2x$  ULN or total bilirubin value  $> 43$   $\mu\text{mol/L}$  (2.5 mg/dL) was observed.

In the open-label extension studies, as in the double-blind studies, when ALT or AST were  $\geq 3x$  ULN, the next dose was to be held. Once ALT and AST were below 3x ULN, tocilizumab treatment was to be restarted at 4 mg/kg and increased to 8 mg/kg when deemed appropriate. The same management guideline was to be followed if indirect bilirubin  $> 2x$  ULN or total bilirubin was  $> 2.5$  mg/dL (43  $\mu\text{mol/L}$ ). Tocilizumab was to be discontinued if: 1) ALT or AST were  $\geq 3x$  ULN after 2 months of treatment with the lower dose, 2) ALT or AST were  $> 5x$  ULN after any one dose of 8 mg/kg, or 3) there was a second bilirubin elevation  $> 2x$  ULN or a total bilirubin of  $> 2.5$  mg/dL (43  $\mu\text{mol/L}$ ).

For all Phase 3 studies, patients withdrawn due to elevated liver function tests were to have repeat testing in 3 to 5 days and then every 2 weeks until the levels decreased. Thereafter, liver function tests were to be monitored on a monthly basis until levels 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.

Doses of MTX or other DMARDs could also be reduced at the discretion of the investigator.

#### **7.6.6.1 *Pattern of ALT and AST Changes Following Administration of Tocilizumab***

Shifts in either ALT or AST from normal to three categories of elevations,  $> \text{ULN}$  to  $3x$  ULN,  $> 3$  to  $5x$  ULN, or  $> 5x$  ULN are summarized in [Table 46](#). In the tocilizumab monotherapy group, ALT and AST shifts occurred less frequently than in the MTX monotherapy group. In the combination therapy studies, 42.8% and 45.9% of patients receiving 4 mg/kg or 8 mg/kg tocilizumab, respectively, shifted from normal to ALT  $> 1$  to  $3x$  ULN, but only 2.5% and 1.3% of this total population had their dose held or discontinued treatment over the study duration. The majority of the shifts in values were to  $> \text{ULN}$  to  $1.5x$  ULN.

**Table 46**                      **Changes in ALT and AST – Double-blind Controlled Studies**

n (%)	TCZ 8 mg/kg N = 288	MTX N=284	TCZ 4mg/kg + MTX N = 774	TCZ 8 mg/kg + DMARD N = 1582	Placebo + DMARD N = 1170
Patients with normal ALT at baseline (n)	269	268	706	1465	1080
ALT >1- 3 xULN	91 (33.8)	86 (32.1)	302 (42.8)	672 (45.9)	206 (19.1)
ALT >3-5 xULN	3 (1.1)	7 (2.6)	28 (4.0)	63 (4.3)	9 (0.8)
ALT > 5 x ULN	2 (0.7)	3 (1.1)	7 (1.0)	20 (1.4)	3 (0.3)
Patients with normal AST at baseline (n)	283	269	743	1502	1123
AST >1- 3 xULN	59 (20.9)	67 (24.9)	241 (32.4)	583 (38.8)	163 (14.5)
AST >3-5 xULN	1 (0.4)	3 (1.1)	7 (0.9)	23 (1.5)	3 (0.3)
AST > 5 x ULN	2 (0.7)	1 (0.4)	0	3 (0.2)	1 (0.1)
% Dose Held**	23 (8.0)	28 (9.9)	19 (2.5)	39 (2.5)	8 (0.7)
% Discontinued**	1 (0.3)	4 (1.4)	10 (1.3)	21 (1.3)	2 (0.2)

\*Percentage of patients that shift from normal at baseline to a worst ALT or AST elevation as calculated with “n” as the denominator.

\*\*Percentage of patients with dose held or discontinued with “N” as the denominator.

In the majority of cases, patient who had shift in ALT or AST values in excess of the ULN were able to recommence treatment after one missed dose. A similar proportion of patients withdrew due to elevated ALT or AST values in each treatment group (Table 46).

Among patients entering with mildly elevated ALT or AST values (< 1.5x ULN at baseline), a higher proportion of patients had a shift in value to > 3x ULN than among patients entering the study with normal transaminase values. ALT shifts to > 3x ULN were observed in 5.5%, 7.8%, and 16.3% of patients in the DMARD, TCZ 4mg/kg + DMARD, and TCZ 8 mg/kg + DMARD groups respectively, while AST shifts to > 3x ULN were seen in 0%, 4.5%, and 6.3%, respectively.

#### **7.6.6.2 Long-term Extension Populations**

Of 2562 patients evaluated in the long-term extension studies, 117 (4.6%) and 53 (2.1%), respectively, experienced single ALT or AST elevations of > 3x ULN. These rates are similar to those observed for MTX alone (3.5% or 2.1%, respectively), the 4 mg/kg + MTX groups (3.5% or 1.2%, respectively), and 8 mg/kg + DMARD groups (4.4% or 1.6%, respectively) of the double-blind studies.

#### **7.6.6.3 Cases of ALT or AST > 3x ULN and Total Bilirubin > 2x ULN**

According to the *Draft FDA Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, patients with a 3-fold or greater elevation above the ULN for ALT or AST who also have elevations in serum total bilirubin to > 2x ULN,

without initial findings of cholestasis (serum alkaline phosphatase activity of > 2x ULN) and where no other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C, pre-existing or acute liver disease, or another drug capable of causing the observed injury, may have an increased risk of liver injury (Hy's Law) [48]. There were two patients in the Phase 3 studies who had > 3-fold transaminase elevations concurrent with > 2-fold total bilirubin elevation, one of whom had gallstones. Both of these patients were reviewed by a panel of hepatologists and are described below.

Patient 4798 (study WA17824, randomized to 8 mg/kg TCZ; study WA18696): During the core study, this 57-year-old female with a RA duration of 9 years had isolated increases of total bilirubin > 1 – 2x ULN (mainly unconjugated) without simultaneous increases in aminotransferases or alkaline phosphatase, suggestive of Gilbert's Disease. She completed the core study and began the long-term extension study, at which time she also began taking MTX 20 mg/week, without any dose titration. Eight weeks later, she had an ALT of 569 U/L (16.7x ULN), AST of 359 U/L (10.6x ULN), total bilirubin of 2.7 mg/dL (2.3x ULN), and indirect bilirubin of 2.2 mg/dL. Tocilizumab was withheld and MTX reduced to 10 mg/week, resulting in lab values returning to within normal levels. She re-initiated tocilizumab at 4 mg/kg and experienced elevations of ALT (166 U/L; > 3x ULN), AST (98 U/L; > 2x ULN) and total bilirubin (1.4 mg/dL; > 1x ULN). She withdrew from the study and aminotransferase and bilirubin levels returned to normal by 12 weeks after her last tocilizumab dose.

Patient 7194 (study WA18063, randomized to 8 mg/kg tocilizumab): This 31-year-old female patient with a RA duration of 9 years had a history of cholelithiasis detected incidentally by ultrasound. On study day 104, while hospitalized for gallstones, her AST was 158 U/L (4.6x ULN) and total bilirubin was 6.6 mg/dL (5.5x ULN). On study day 112, she underwent a cholecystectomy. Elevated AST and total bilirubin returned to normal as recorded on study day 141. The patient continued in the study.

### **7.6.7 Infusion Reactions**

Tocilizumab was administered as a 100 mL solution infused over 1 hour every 4 weeks. The placebo control solution consisted of 5% sucrose and 0.005% Polysorbate 80 in water and was administered only in the double-blind study trials. In the open-label extension, there was no control group. Infusion-associated adverse events were reported according to the time when they occurred (ie, whether the event occurred during an infusion or within the first 24 hours following an infusion). Events that might have been due to a hypersensitivity reaction were pre-defined using MedDRA AE Grouping Terms ([Appendix 20](#)). These two sets of data were summarized separately as well as pooled into a total data set.

In the pooled data from the double-blind period, there were no substantive differences in infusion-associated adverse events between the various tocilizumab dose groups so the pooled tocilizumab-treated patients (N=2644) are compared here to the placebo-treated (N=1170) and MTX-treated (N=284) patients. Infusion-related events occurred in 7.6% of patients in the tocilizumab 4 mg/kg + MTX group, 6.9% of patients in the tocilizumab 8 mg/kg + DMARD group, 8% of patients in the tocilizumab monotherapy group, and in 7.3% of patients in the Total Safety Exposure group.

There was an increase in the percentage of tocilizumab-treated patients (7.3%) compared with placebo-treated (5.1%) or MTX-treated patients (4.6%) experiencing infusion-associated adverse events in the pooled dataset that included the infusion period and the subsequent 24 hours. The only infusion-associated adverse events that occurred in >1% of the tocilizumab-treated patients were headache (TCZ, 1.6%; placebo, 1.1%; MTX, 0.4%), a variety of skin disorders (such as rash, pruritus, and urticaria) (TCZ, 1.6%; placebo, 0.5%; MTX, 0.4%), and hypertension (TCZ, 1.2%; placebo, 0.9%; and MTX, 0.7%). Sixty-seven percent of all infusion-associated events occurred in the first two infusion periods.

Serious infusion reactions were observed in eight cases, of which six occurred following the second or third infusion of tocilizumab 4 mg/kg. Eight patients in the tocilizumab treatment groups withdrew for allergic dermatitis (1), syncope (1), hypersensitivity (1), infusion-related reaction (2), and anaphylactic reaction (3).

Tocilizumab is similar to other biological therapies in causing these reactions and should be administered in the proper clinical setting with treatment available for possible hypersensitivity reactions.

#### **7.6.8 Immunogenicity**

Serum was screened for human anti-human antibodies (HAHAs) that recognize tocilizumab and confirmed with a sandwich ELISA assay with displacement of the bound anti-tocilizumab HAHAs. All samples that were positive for anti-tocilizumab HAHAs were then tested to see whether the antibody was capable of interfering with the binding of tocilizumab to the sIL-6 receptor (neutralizing assay). Immunoglobulin isotypes were also characterized in a BiaCore assay.

All patients in the double-blind studies were tested for anti-tocilizumab HAHAs at week 0 and week 24 or withdrawal and every 24 weeks thereafter in the long-term extension studies. In addition, for patients with anti-tocilizumab HAHAs at week 24, serum from weeks 4, 8, and 12 were analyzed. Patients who experienced infusion-related adverse events or withdrew because of such events also had testing of serum taken prior to these events.

A total of 3353 patients, 2876 patients in the double-blind trials and 477 patients in the open-label extension studies, were screened for anti-tocilizumab HAHAs. Forty-six patients in the double-blind studies tested positive. The percentages of patients with anti-tocilizumab HAHAs were similar for the three pooled tocilizumab treatment groups: 2.3% for the 4 mg/kg + MTX group, 1.6% for the 8 mg/kg + D MARD group, and 0.5% for the 8 mg/kg group. In addition, 13 patients in the open-label studies tested positive for a total of 59/3353 patients, 1.8% of the entire tested population; in 1.1% of the tested population, the antibody was positive in the neutralizing assay.

Ten of 160 patients who experienced infusion-related adverse events had anti-tocilizumab HAHAs in the double-blind studies. Five of these HAHA positive patients discontinued treatment (3 patients who received tocilizumab 4 mg/kg and 2 who received tocilizumab 8 mg/kg). Five of 8 patients who experienced serious adverse events or withdrew because of infusion reactions and who were tested for anti-tocilizumab HAHAs were positive for

anti-tocilizumab IgG and IgM antibodies, and three for neutralizing anti-tocilizumab HAHAs.

The development of neutralizing antibody was not associated with changes in CRP and DAS28. Only one patient who developed anti-tocilizumab antibodies withdrew due to lack of efficacy.

In conclusion, anti-tocilizumab HAHAs develop in few patients, 1.8% of the total tested population. About 64% of the HAHAs are neutralizing, but there is limited evidence that the degree of interference is sufficient to negate the effects of tocilizumab in vivo. Most patients who reported a serious infusion reaction did not have detectable antibody.

## **7.7 Adverse Events by Subgroup**

The adverse event profile of tocilizumab was not notably different across the demographic subgroups defined by age, gender, region, race, weight, and body mass index.

## **7.8 Clinical Safety Summary and Recommendations**

The summary of key safety findings is as follows:

- Tocilizumab was generally well tolerated as monotherapy and in combination with MTX or other non-biologic DMARDs.
- Many of the adverse events reported are consistent with the known mechanism of action of tocilizumab.
- The rates of serious infections were 3.75 events per 100 patient-years in the placebo/DMARD group, 4.35 in the tocilizumab 4 mg/kg + DMARD group, and 5.18 in the tocilizumab 8 mg/kg + DMARD group and these rates did not increase over time.
- In the Phase 3 double-blind program, 3 patients treated with tocilizumab and no patients in the comparator groups had GI perforations. Ten additional patients had GI perforations that occurred beyond 24 weeks.
- The observed decrease in neutrophils is dose-dependent, occurred largely within the normal range, and was reversible upon discontinuation of tocilizumab.
- LDL levels increased in both the tocilizumab 4 mg/kg and 8 mg/kg treatment groups and responded appropriately to statin therapy.
- Rates of myocardial infarction and stroke were similar across treatment groups in the double-blind studies and did not increase over time.
- Most ALT and AST elevations were transient and returned to normal without dose adjustment or treatment discontinuation. Elevated transaminases were not associated with abnormal liver function and no serious adverse events were associated with the transaminase elevations. In 4142 patient-years of exposure there were no patients who met the criteria of Hy's Law.
- In the 6-month, double-blind studies, the rate of malignant neoplasms was 1.33 events per 100 patient-years and 1.27 in the tocilizumab and control groups, respectively. Following longer-term treatment, the rate in the total Phase 3 population was 1.45 events per 100 patient-years; excluding non-melanoma skin cancers, the rate was

- 0.91 per 100 patient-years. Despite the low event rate, a potential risk for individual tumor types cannot be excluded at this time.
- Serious infusion reactions were uncommon; most of these events occurred after the second or third infusion of tocilizumab.
  - Anti-tocilizumab antibody was detected in < 2% of patients. In general, the emergence of antibody was not associated with either loss of efficacy or a deterioration in the safety profile.

Recommendations:

- Management of cardiovascular risk should include:
  - Assessment and treatment of fasting lipids after 12 weeks of tocilizumab therapy, even if the patient is on a lipid-lowering agent at baseline.
  - Patients should be treated to target lipid levels according to local clinical guidelines.
- Tocilizumab should not be administered in patients with an active infection.
- Tocilizumab should be interrupted if a patient develops a serious infection or an infection that could become serious, until the infection is resolved.
- Exercise caution in individuals with a higher risk of infection (eg, diabetics, history of recurrent infection).
- Tuberculosis screening is recommended prior to initiation of tocilizumab.
  - If positive for tuberculosis, treatment should be initiated according to clinical practice guidelines.
- Live attenuated vaccines should not be given concurrently with tocilizumab.
- Liver function (ALT and AST) should be monitored following initiation of therapy and periodically thereafter.
- Tocilizumab should not be administered to patients with a history of complicated diverticulitis and should be used with caution in patients with a history of diverticulitis. Patients should be warned to contact a physician if they develop the signs and symptoms of diverticulitis (eg, abdominal pain, a change in bowel habit, or GI bleeding).
- Tocilizumab should be administered in the proper clinical setting with treatment available for possible hypersensitivity reactions.

## **8. RISK ASSESSMENT AND MANAGEMENT**

The overall risk assessment and management plan consists of a series of prospective, observational cohort studies as well as targeted and routine activities coordinated through a central company team. The planned studies and activities will supplement the 5-year, long-term extension studies, and will consist of a series of US and European general RA registries, pregnancy registries (US and European), targeted pharmacovigilance (such as guided questionnaires), and routine risk assessment and management activities. In addition, claims and medical record databases will be utilized as patient numbers grow in these databases.



## 8.1 Long-Term Extension Studies

Roche has extended the duration of three long-term safety studies are available for long-term follow-up of tocilizumab-treated patients under close, structured safety monitoring and assessment of adverse events of interest. These studies are the uncontrolled study period of study WA17823, and the open-label extension studies WA18695 and WA18696. These studies will accrue data from > 2500 patients for up to 5 years. Data will be analyzed at 6-month intervals for up to 5 years.

## 8.2 US and European Registries

It is planned to add a tocilizumab-treated cohort to existing post-marketing registries including a large US general registry of RA patients and three dedicated, independent biologics registries in Europe. The European registries are the British Society for Rheumatology Biologics Registry (BSRBR), the Swedish biologics registry, ARTIS, and the German registry, RABBIT. In addition, there will be a large US disease registry. The planned studies will be conducted in these well-established registries; no new registries will be created. The target study population size will be 5000 in the US and over 5000 patients in Europe, with an anticipated study duration of 5 years. This will provide approximately 25000 years of follow-up experience on each continent. The table below shows power calculations considering each continent separately, based on the projected study size of 25000 person-years, a target detectable risk of 2-fold, and a target power of 80%.

Simple Power calculations, assuming 5,000 patients followed for 5 years					Power calculation assuming 20% loss to followup	
Event	Background Rate	Detectable Risk given ≥80% Power	Power of Detecting an RR ≥ 2	Power of Detecting an RR ≥ 3	Power of Detecting Hazard Ratio ≥ 2	Power of Detecting Hazard Ratio ≥ 3
MI	5.3 per 1000 pys*	2-fold	≥80%	≥80%	≥80%	≥80%
Stroke	5.1 per 1000 pys*	2-fold	≥80%	≥80%	≥80%	≥80%
Hospitalized Infections	3864.3 per 100,000**	2-fold	≥80%	≥80%	≥80%	≥80%
Malignancies	1295.6 per 100,000***	2-fold	≥80%	≥80%	≥80%	≥80%
lung	228.8 per 100,000***	2-fold	≥80%	≥80%	76%	≥80%
lymphoma	91.7 per 100,000***	2.5 fold	76%	≥80%	39%	≥80%
NHL	85.5 per 100,000***	2.5 fold	76%	≥80%	37%	≥80%
stomach	8.1 per 100,000***	6.5 fold	13%	30%	7%	14%
cervix	8.2 per 100,000***	6.5 fold	13%	30%	7%	14%
GI perforations	1.32 per 1000****	2-fold	≥80%	≥80%	52%	≥80%
Serious Liver events (eg decompensation)	1.0 per 1000*****	2-fold	≥80%	≥80%	42%	≥80%
Liver events (Fibrosis and cirrhosis)	5.56 per 1000*****	2-fold	≥80%	≥80%	≥80%	≥80%

\*Solomon et al. 2006

\*\*Smitten et al. 2008

\*\*\*Wolfe and Michaud 2007

\*\*\*\*UHC analysis, 2008

\*\*\*\*\*Beyeler et al. 199

On the basis of previous experience in these registries, a 3-year accrual time is envisaged. The table above also includes allowances for accrual time and for a 20% loss to follow-up. The registry studies will not only include patients treated with tocilizumab, but will also include control cohorts of RA patients who are receiving other therapies to provide comparison data for the accruing safety information for tocilizumab.

Patients in these registries will be prescribed tocilizumab or other therapy by participating physicians in a 'usual care' setting and will be eligible to join within the first 6 months of initiating therapy. Patients who have already been enrolled in a registry while treated with

another agent will be eligible to join the tocilizumab cohort on initiating tocilizumab treatment. The ratio of comparison patients to tocilizumab patients will be 1.5 or 2 to 1, depending on the registry. Comparison groups will consist of patients who are receiving non-biologic DMARDs and, where an anti-TNF comparison group is available, this group will also be studied.

Because the registries that Roche will be joining for tocilizumab are already well-established, each already has a defined set of practices and possibilities with regard to questions that may be asked, populations that may be followed, and processes for reporting. For this reason, the study protocols will differ in some regards between registries. It is generally not considered possible to pool data across RA registries because each registry has its own set of procedures, although this discussion has in fact been a topic of interest among the registries themselves. However, the set of questions used as a point of departure for each registry study will be the same; these questions will cover the adverse events of interest outlined in the safety section of this document with the exceptions noted below.

As the focus of the registries is on collection of clinical data for safety concerns relating to laboratory abnormalities, clinical correlates have been defined for collection. This includes liver events, cardiovascular events such as MI and stroke, and serious infections. The registries already have considerable experience in collecting information on serious infections and malignancies, as these events have been of interest for other biologic therapies. Cardiovascular events have also been intensively studied in these registry populations.

The registries all provide for the collection of baseline information on patients, to include among other factors, disease duration, current HAQ-DI, current significant comorbidities, and all relevant previous therapies. The registries also have procedures for collecting follow-up information on a 6 month (or more frequent) basis. The European registries have links to their respective national death and cancer registries. All of the registries also collect hospital discharge information. This information will be provided to Roche on a 6-monthly basis in the form of aggregate data listings. In addition, the registries will provide analyses of the data they have collected at the conclusion of the study, and also at an agreed upon interim date. Roche will not receive individual identifiable data for any patients beyond what they see as part of their own safety reporting process; procedures are in place in each registry for timely reporting of serious adverse events.

In addition to the general registries, Roche will participate in pregnancy registries in order to identify at an early date any safety issues related to teratogenicity, and is working with the Organization of Teratology Information Specialists in the US and European Network of Teratology Information Services (ENTIS). Both are established pregnancy registries that have a dedicated project area for Autoimmune Diseases in Pregnancy. There are currently nine pharmaceutical sponsors of this project. Women who are less than 20 weeks into their pregnancy can enroll in the project. They are queried three times during their pregnancy and all live born offspring are given a standardized physical examination. Again, two control groups of women receiving other therapies are planned. Roche will also be collecting information on safety during pregnancy through the pregnancy questionnaire that is part of the BSRBR protocol, through the pregnancy

outcome (congenital malformations and perinatal morbidity and mortality from the national birth registry) reporting provided through ARTIS, and through periodic specific queries to members of ENTIS. ENTIS registries follow approximately 3300 pregnancies per year in Europe and are sponsored by their local and federal authorities. They are not allowed to provide listings directly to pharmaceutical companies, however, they are able to respond to queries with general statements reporting on any risk that has been identified.

### **8.3 Claims Data Analyses**

Events of interest will also be examined on a periodic bases in large claims databases, once patient experience with tocilizumab begins to be reflected in these resources. These resources will offer another opportunity to monitor the safety of tocilizumab once it is on the market.

### **8.4 Targeted (Enhanced) Pharmacovigilance**

Guided questionnaires have been designed for a number of the events of special interest for tocilizumab.

## **9. BENEFIT RISK STATEMENT**

Serum and articular IL-6 levels are increased in RA patients, which accounts for many of the systemic and articular manifestations of the disease. Tocilizumab's unique mechanism of action of competitively blocking both mIL-6R and sIL-6R offers a new approach to the management of RA and offers clinically meaningful benefits to patients who may not respond adequately to existing therapies.

The clinical benefits of tocilizumab were demonstrated in a broad patient population including patients who are naïve to treatment and patients who have inadequately responded or were intolerant to DMARDs or currently available biologic treatments. Of particular note are the substantial numbers of patients in the Phase 3 trials achieving clinically meaningful improvements in signs and symptoms (ACR50, ACR70, DAS28 remission) as well as important benefits described by patient-reported outcomes. The clinical benefit achieved in these trials has been sustained as patients continue treatment in the open-label extension trials.

Important differences were noted between the tocilizumab dose regimens with regard to the proportion of patients achieving clinically important improvements as measured by ACR50 response, ACR70 response, and DAS28 remission. The 8 mg/kg dose controlled inflammation throughout the dosing period, as indicated by the continuous suppression of CRP to levels within the normal range at the first time point measured. In contrast, the tocilizumab 4 mg/kg dose resulted in only intermittent CRP suppression in all studies. These clinical data are supported by pharmacokinetic/pharmacodynamic analyses demonstrating that the tocilizumab exposure required to attain CRP normalization, good EULAR response, and DAS28 remission is more readily achieved by the tocilizumab 8 mg/kg dose.

Tocilizumab is highly specific for sIL-6R and mIL-6R. The efficacy and safety profile of tocilizumab are a consequence of the antagonism of IL-6 actions in RA patients. IL-6 is a primary mediator of the acute phase response which is responsible for the induction or

suppression of specific processes within the liver. Many of the clinical effects of elevated IL-6 are observed in patients with RA. Tocilizumab administration reverses many of these effects.

Inhibition of IL-6 decreases inflammatory mediators and will alter hepatic protein synthesis. Total cholesterol, HDL, LDL, and triglycerides increase as inflammation decreases following initiation of tocilizumab. The pattern of decreased inflammation and increased serum LDL has also been observed with anti-TNF therapy, although the magnitude of the LDL increase is greater with tocilizumab. The incidence of cardiovascular and cerebrovascular events observed to date with tocilizumab is low, consistent with the potential that control of inflammation is important with respect to reducing cardiovascular risk.

Elevations in hepatic transaminases are observed following treatment with tocilizumab. The majority of these elevations were transient, single occurrences that returned to normal values without tocilizumab dose adjustment or treatment discontinuation. The elevations in transaminases were not associated with clinical evidence of abnormal liver function. Patients in the studies are currently being followed long-term with monitoring of hepatic transaminases at 12 week intervals, unless more frequent assessment is warranted by the treating physician. Dose modification is recommended for elevations to > 3 times the ULN. When administered with other DMARDs such as MTX, dose modifications may be required at levels between 1-3 times the ULN, as recommended in the prescribing information or treatment guidelines from professional organizations. Roche recommends that monitoring of transaminases be based on clinical considerations and in accordance with practice guidelines specific to additional RA medications (eg, MTX).

As IL-6 plays a central role in the immune response to pathogenic organisms, it is expected that treatment with tocilizumab may play a role in the host response to infection. The incidence of serious infection following treatment with tocilizumab (4.45 events per 100 patient-years for 8 mg/kg) is higher than in the control population (3.66 events per 100 patient-years). Pneumonia and soft tissue infections, such as cellulitis, were the most frequent types of infection observed. Most responded to appropriate IV antibiotic therapy, although a small number of patients died. The signs and symptoms of infection may be more subtle in patients on tocilizumab and requires good communication between the patient and their healthcare provider. Roche recommends that:

- Tocilizumab treatment not be initiated in patients with active infections and that administration should be interrupted if a patient develops a serious infection, until the infection is controlled.
- Physicians pay particular attention to the signs and symptoms of infection in patients who are at increased risk for infections, including those with comorbid diabetes mellitus.
- Treating physicians are advised to exercise caution when considering the use of tocilizumab in patients with a history of recurring serious infection. Early diagnosis and aggressive management of infections is recommended.

Neutrophil counts are reduced in patients receiving tocilizumab with Grade 3 neutropenia occurring in 1-3% of tocilizumab-treated patients. Therefore, a patient's "on treatment neutrophil count" should be taken into consideration in the diagnosis of an early infection.

The gastrointestinal perforations observed were mostly complicated diverticulitis. The risk of these events has been reported to be increased in patients taking NSAIDs or corticosteroids and in patients with connective tissue disease. These events have been reported with MTX and other biological therapies for RA. Whether tocilizumab therapy confers an independent risk and whether this is quantitatively different from other biological therapies for RA is being investigated. Patients should be warned to contact a physician if they develop the signs and symptoms of diverticulitis (eg, abdominal pain, a change in bowel habit, or GI bleeding).

Demyelinating disorders have been reported in association with biological therapies for RA. Although there is no evidence for an association between demyelinating disorders and tocilizumab from the clinical program to date, this cannot be determined until much greater exposure accrues.

The risk of malignancy is similar to the background rate in a RA population. The data from the studies performed to date, while not indicating an increased risk of malignancy, are not sufficient to determine if a link exists between tocilizumab and the development of cancer. Continued surveillance of patients on tocilizumab will be necessary.

Infusion reactions and the development of anti-tocilizumab antibodies affecting efficacy and safety were rare.

In this comprehensive clinical program with a large safety database, tocilizumab 8 mg/kg was generally well tolerated. Tocilizumab has a well characterized adverse event profile. Adverse effects noted during the clinical program are recognizable, reversible, and usually not treatment-limiting.

In summary, the benefits of tocilizumab therapy in earlier stage RA and inadequate responders to DMARDs and to anti-TNF agents has been demonstrated. The adverse event profile will require the management of infections and hepatic transaminases, in which rheumatologists have considerable experience. The overall benefit/risk assessment of tocilizumab in patients with RA is favorable. Tocilizumab provides a new therapeutic option for patients with moderately to severely active RA who are naïve to treatment with, or who had an inadequate response to, one or more DMARDs or TNF antagonists.

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## 11. APPENDICES

### Appendix 1 ACR Responses for Phase 2 Study LRO301

	Placebo + MTX N = 49	TCZ 2 mg/kg N = 53	TCZ 4 mg/kg N = 54	TCZ 8 mg/kg N = 52	TCZ 2 mg/kg + MTX N = 52	TCZ 4 mg/kg + MTX N = 49	TCZ 8 mg/kg + MTX N = 50
ACR20	41%	31%	61%	63%	64%	63%	74%
p-value			<0.05	<0.05	<0.05	<0.05	<0.001
ACR50	29%	6%	28%	41%	32%	37%	53%
p-value							<0.05
ACR70	16%	2%	6%	16%	14%	12%	37%
p-value							<0.05

All comparisons are tocilizumab versus MTX.

### Appendix 2 Summary of Primary and Secondary Endpoints in the Phase 3 Studies

Endpoint at week 24	DMARD Inadequate Responders				TNF Inadequate Responders		Monotherapy	
	WA17822		WA17823		WA18063	WA18062		WA17824
	4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg	8 mg/kg
ACR20	√	√	√	√	√	√	√	√
ACR50	√	√	X	√	√	X	√	√
ACR70	√	√	X	√	√	X	√	√
ACR Components	√	√	X	√	√	X	√	No non-inferiority margin predefined
DAS28	√	√	√	√	√	√	√	
DAS28 < 2.6	√	√	X	√	√	X	√	
EULAR Response	√	√	X	√	√	X	√	
Hemoglobin	√	√	X	√	√	X	√	
FACIT-F	√	√	X	X	√	X	X	
SF-36 PCS/MCS	√	√	X	X	√	X	X	

√ – tocilizumab statistically superior to control.

Adjusted for multiplicity using a predefined hierarchy.

PCS=physical component score; MCS=mental component score

### Appendix 3 Cross-Study Presentation of ACR20 Responses at Week 24 (ITT Population)

Endpoint	WA17822			WA17823			WA18063	
	Placebo + MTX N = 204 n (%)	TCZ 4 mg/kg + MTX N = 213 n (%)	TCZ 8 mg/kg + MTX N = 205 n (%)	Placebo + MTX N = 393 n (%)	TCZ 4 mg/kg + MTX N = 399 n (%)	TCZ 8 mg/kg + MTX N = 398 n (%)	Placebo + DMARD N = 413 n (%)	TCZ 8 mg/kg + DMARD N = 803 n (%)
Primary – ACR20	54 (26.5%)	102 (47.9%)	120 (58.5%)	106 (27.0%)	202 (50.6%)	224 (56.3%)	101 (24.5%)	488 (60.8%)
p-value		<0.0001	<0.0001		<0.0001	<0.0001		<0.0001
ACR50	22 (10.8%)	67 (31.5%)	90 (43.9%)	38 (9.7%)	100 (25.1%)	128 (32.2%)	37 (9.0%)	302 (37.6%)
p-value		<0.0001	<0.0001		<0.0001*	<0.0001		<0.0001
ACR70	4 (2.0%)	26 (12.2%)	45 (22.0%)	8 (2.0%)	44 (11.0%)	50 (12.6%)	12 (2.9%)	165 (20.5%)
p-value		<0.0001	<0.0001		<0.0001*	<0.0001		<0.0001
DAS28 < 2.6	1 (0.8%)	21 (13.5%)	47 (27.5%)	8 (3.8%)	54 (17.8%)	105 (33.3%)	11 (3.4%)	216 (30.2%)
p-value		0.0002	<0.0001		0.0002*	<0.0001		<0.0001

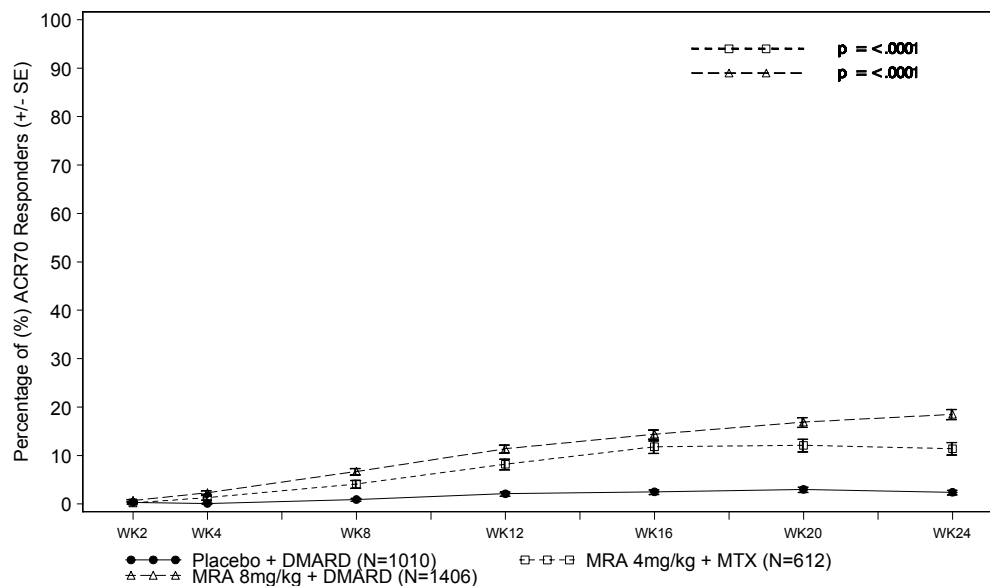
P-values calculated from Cochran-Mantel-Haenszel analysis

All comparisons to placebo

\* Due to a break in the hierarchical testing of the secondary endpoints, this cannot be considered as statistically significant.

## Appendix 4 ACR70 Response Rates by Visit – DMARD IR ITT Population

EGacr70pli ACR70 Response Rates by Visit- 6 Month Pooled Data (ITT Population)



Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons to placebo + DMARD. LOCF used for joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Program : \$PROD/cd11935h/EGacr.sas / Output : \$PROD/cd11935h/reports/EGacr70pli.cgm  
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## Appendix 5 Components of ACR Response at Week 24, Percentage Change at Week 24 Compared to Baseline- DMARD IR (ITT Population)

Efficacy Parameter Week 24	Placebo + DMARD (N=1010)	MRA 4mg/kg + MTX (N=612)	MRA 8mg/kg +DMARD (N=1406)
ACR20 Response(a)	25.8%	49.7%***	59.2%***
ACR50 Response(a)	9.6%	27.3%***	37.0%***
ACR70 Response(a)	2.4%	11.4%***	18.5%***
TJC Mean % Change (b)	-20.2%	-48.0%***	-52.4%***
SJC Mean % Change (b)	-19.0%	-47.5%***	-51.6%***
Pain VAS (b)	-6.4%	-31.6%***	-36.7%***
Patient Global Assessment (b)	-14.3%	-36.6%***	-40.7%***
Physician Global Assessment (b)	-40.4%	-51.8%***	-60.4%***
HAQ-DI (b)	-15.0%	-32.0%***	-33.8%***
CRP (b)	45.8%	-4.9%***	-84.0%***

(a) P-values from Cochran-Mantel-Haenszel analysis

(b) P-values from an Analysis of Variance of the Change from Baseline

\*Comparison with Placebo + MTX arm within same study (2-sided) p<=0.05

\*\*Comparison with Placebo + MTX arm within same study (2-sided) p<=0.01

\*\*\*Comparison with Placebo + MTX arm within same study (2-sided) p<=0.0001

The stratification factor by study is included in the model

LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP was used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non-Responder'.

MRA 4mg/kg + MTX pooled data from WA17822 and WA17823. MRA 8mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063.

Program : \$PROD/cd11935h/etcompacr.sas

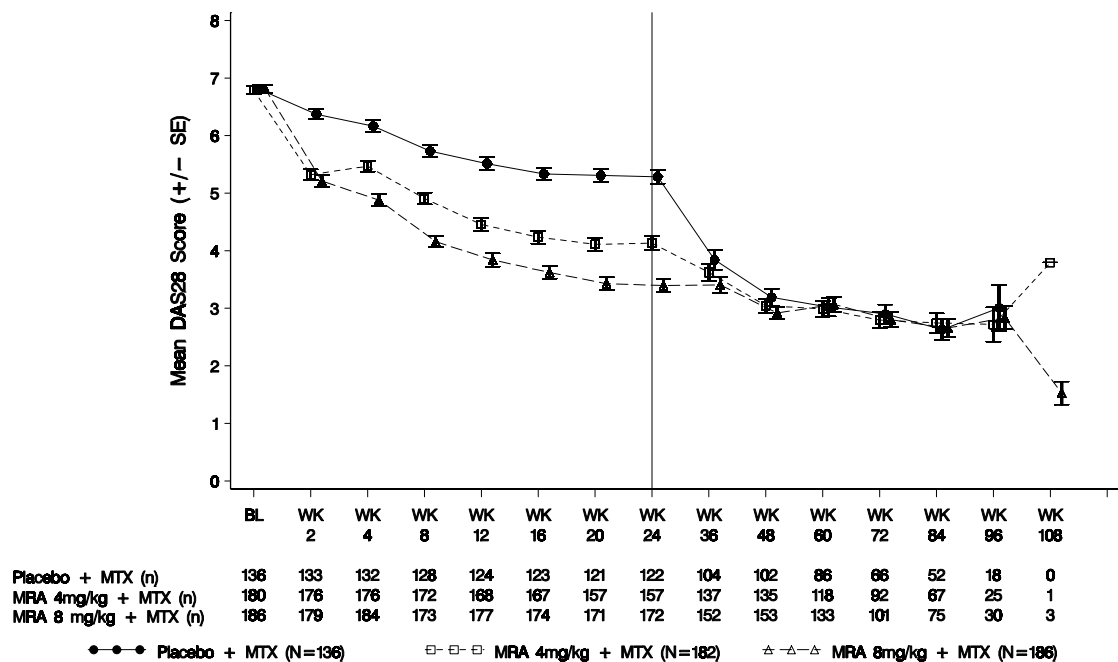
Output : \$PROD/cd11935h/reports/etcompacrpooli.rpt8

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## Appendix 6 Plot of Mean DAS28 Score Calculated using ESR by Visit – WA17822 Study Group (ITT Population)

EGpDASesrwa17822 Plot of Mean DAS28 Score Calculated using ESR by Visit – WA17822 Study Group (ITT Population)

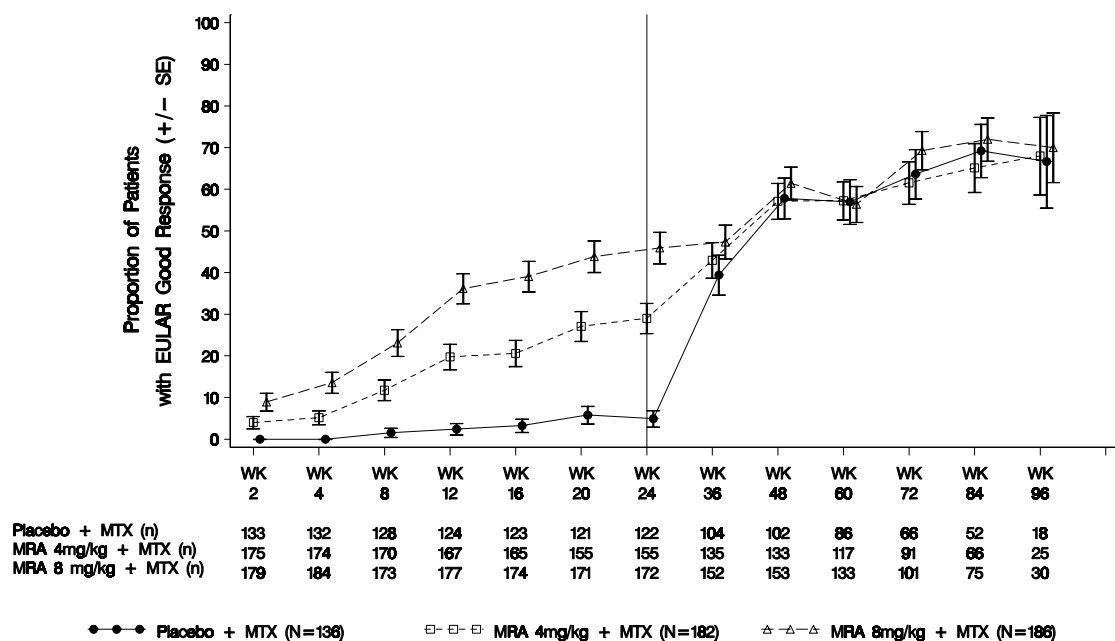


LOCF used for tender and swollen joint counts. No imputation used for ESR and Patient's Global Assessment of Disease Activity VAS.  
 Escape patients are excluded.

Program :/opt/BIOSTAT/prod/cd11935m/m11935aEGpDAS.sas / Output :/opt/BIOSTAT/prod/cd11935m/m11935a/reports/EGpDASesrwa17822L.ogm  
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## Appendix 7 Proportion of Patients with EULAR Good Response by visit – WA17822 Study Group (ITT Population)

EG\_Eular50wa17822 Plot of Proportion of Patients with EULAR Good Response by Visit –WA17822 Study Group (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/cd11935m/mt1935aEG\_Eular.sas / Output :/opt/BIOSTAT/prod/cd11935m/mt1935a/reports/EG\_Eular50wa17822l.cgm  
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## Appendix 8      Components of ACR Response at Week 24, Percentage Change at Week 24 Compared to Baseline: Anti-TNF-Inadequate Responders (ITT Population) (WA18062)

Efficacy Parameter Week 24	Placebo + MTX (N=158)	TCZ 4mg/kg + MTX (N=161)	TCZ 8mg/kg +MTX (N=170)
TJC Mean % Change	9.8%	-33.3%***	-46.3%***
SJC Mean % Change	7.9%	-31.6%***	-35.8%***
Pain VAS	-9.2%	-19.0%	-43.1%
Patient Global Assessment	-24.8%	-26.8%	-41.3%
Physician Global Assessment	-24.6%	-41.1%*	-55.3%***
HAQ-DI	-0.9%	-18.8%**	-25.0%**

P-values from an Analysis of Variance of the Change from Baseline

\*Comparison with Placebo + MTX arm within same study (2-sided)  $p \leq 0.05$

\*\*Comparison with Placebo + MTX arm within same study (2-sided)  $p \leq 0.01$

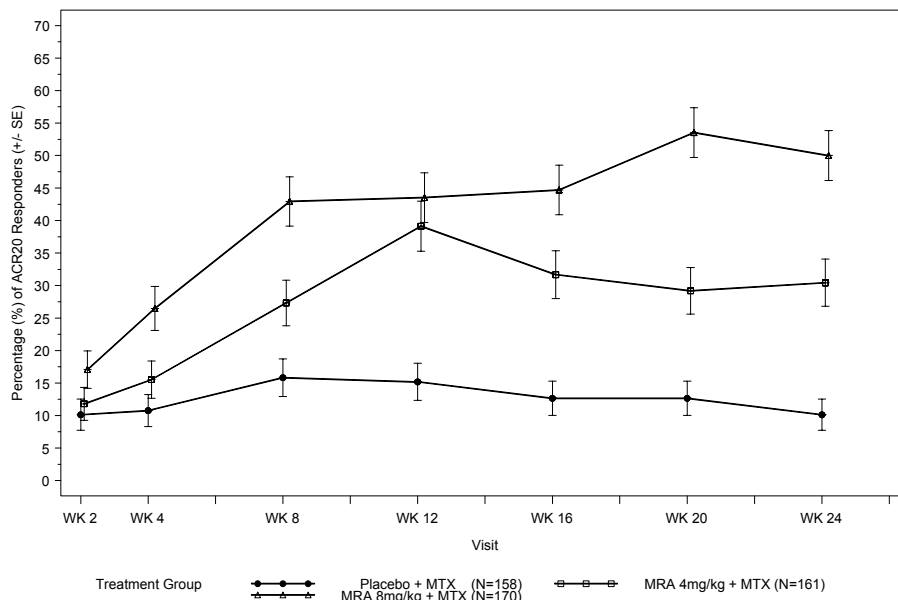
\*\*\*Comparison with Placebo + MTX arm within same study (2-sided)  $p \leq 0.0001$

LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP was used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non-Responder'. Analysis stratified by site



## Appendix 9 ACR20 Response Rates by Visit – Anti-TNF IR

efpercseacr2i ACR20 Response Rates by Visit (ITT Population)

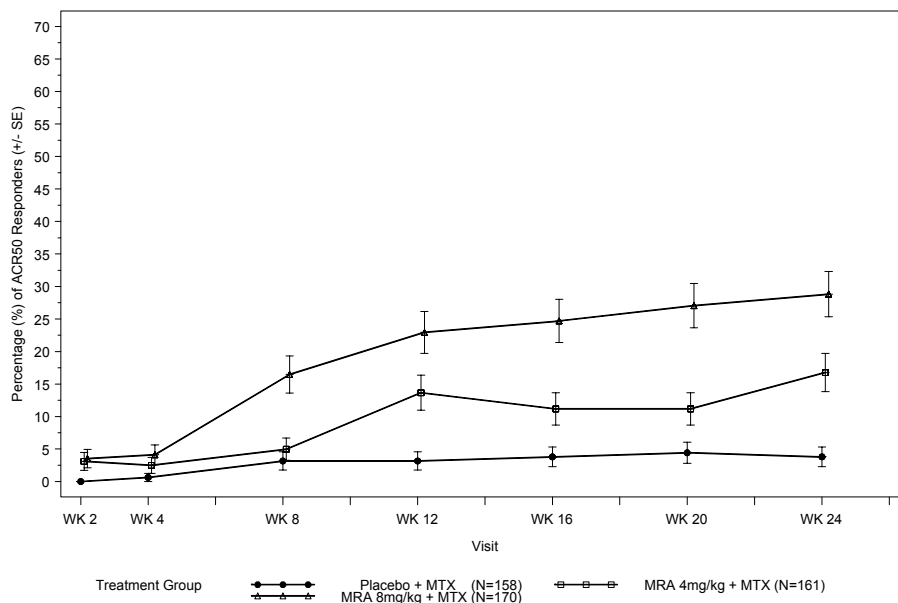


LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Program : \$PROD/cdp11935/wa18062/efpercseacr.sas / Output : \$PROD/cdp11935/wa18062/reports/efpercseacr2i.cgm  
11JUN2007 13:55

## Appendix 10 ACR50 Response Rates by Visit – Anti-TNF IR

efpercseacr5i ACR50 Response Rates by Visit (ITT Population)

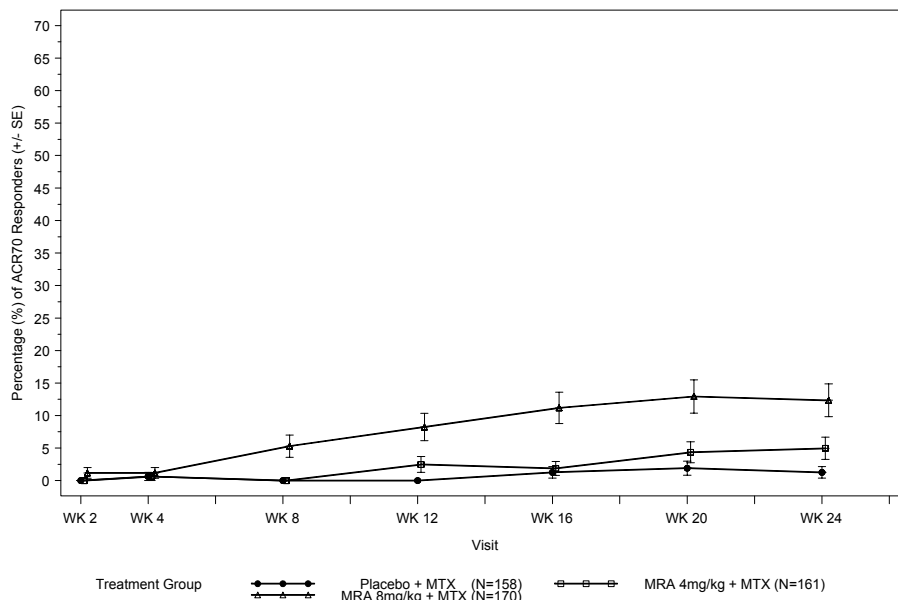


LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Program : \$PROD/cdp11935/wa18062/efpercseacr.sas / Output : \$PROD/cdp11935/wa18062/reports/efpercseacr5i.cgm  
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## Appendix 11 ACR70 Response Rates by Visit – Anti-TNF IR

efpercseacr7i ACR70 Response Rates by Visit (ITT Population)



LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Program : \$PROD/cdp11935/wa18062/efpercseacr.sas / Output : \$PROD/cdp11935/wa18062/reports/efpercseacr7i.cgm  
11JUN2007 13:55

## Appendix 12 Analysis of Variance of Change from Baseline in SF-36 Physical Component Summary Score at Week 24 – TNF IR (ITT Population)

	Placebo + MTX (N=158)	MRA 4mg/kg + MTX (N=161)	MRA 8mg/kg + MTX (N=170)
n	61	104	121
Adjusted Mean	2.22	7.09	8.02
Difference		4.87	5.80
95% CI for difference		(1.81, 7.93)	(2.68, 8.92)
p-value		0.0020	0.0003

All comparison(s) to Placebo + MTX.

No imputation used for missing score.

All assessments are set to missing from the time a patient receives escape therapy.

The norm based scores are reported in this table.

Positive change indicates a better health state.

Program : \$PROD/cdp11935/etanvarqol.sas

Output : \$PROD/cdp11935/wa18062/reports/etanvarqol36pwk24i.rp8

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## Appendix 13 Analysis of Variance of Change from Baseline in SF-36 Mental Component Summary Score at Week 24 (ITT Population)

	Placebo + MTX (N=158)	MRA 4mg/kg + MTX (N=161)	MRA 8mg/kg + MTX (N=170)
n	61	104	121
Adjusted Mean	4.07	4.46	4.06
Difference		0.39	-0.01
95% CI for difference		(-4.03, 4.81)	(-4.51, 4.50)
p-value		0.8627	0.9966

All comparison(s) to Placebo + MTX.  
No imputation used for missing score.  
All assessments are set to missing from the time a patient receives escape therapy.  
The norm based scores are reported in this table.  
Positive change indicates a better health state.

Program : \$PROD/cdpl1935/etanvarqol.sas  
Output : \$PROD/cdpl1935/wa18062/reports/etanvarqol36mwk24i.rp8  
11JUN2007 14:08

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## Appendix 14 Components of ACR Response at Week 24, Percentage Change at Week 24 Compared to Baseline - WA17824, All Patients Excluding Placebo Patients (PP Population)

Efficacy Parameter Week 24	MTX (N=259)	MRA 8mg/kg (N=265)
TJC Mean % Change	-43.9%	-53.7%
SJC Mean % Change	-39.8%	-55.7%
Pain VAS	-45.0%	-45.0%
Patient Global Assessment	-42.7%	-46.0%
Physician Global Assessment	-45.4%	-60.4%
HAQ-DI	-30.9%	-45.3%
CRP	-29.4%	-76.8%

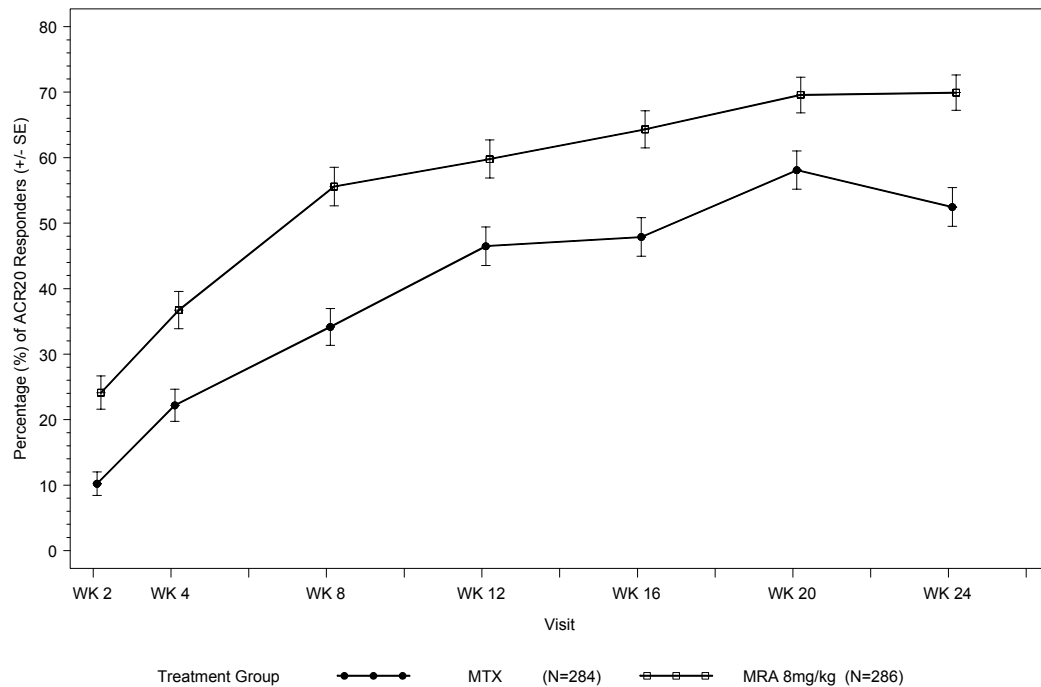
LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP was used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non-Responder'. Analysis stratified by site

Program : \$PROD/cd11935h/etcompacrgrp3.sas  
Output : \$PROD/cd11935h/reports/etcompacrgrp3i.r18  
02AUG2007 11:50

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## Appendix 15 ACR20 Response Rates by Visit – Monotherapy Study

efpercseacr\_502i ACR20 Response Rates by Visit - All Patients excluding Placebo Patients (ITT Population)

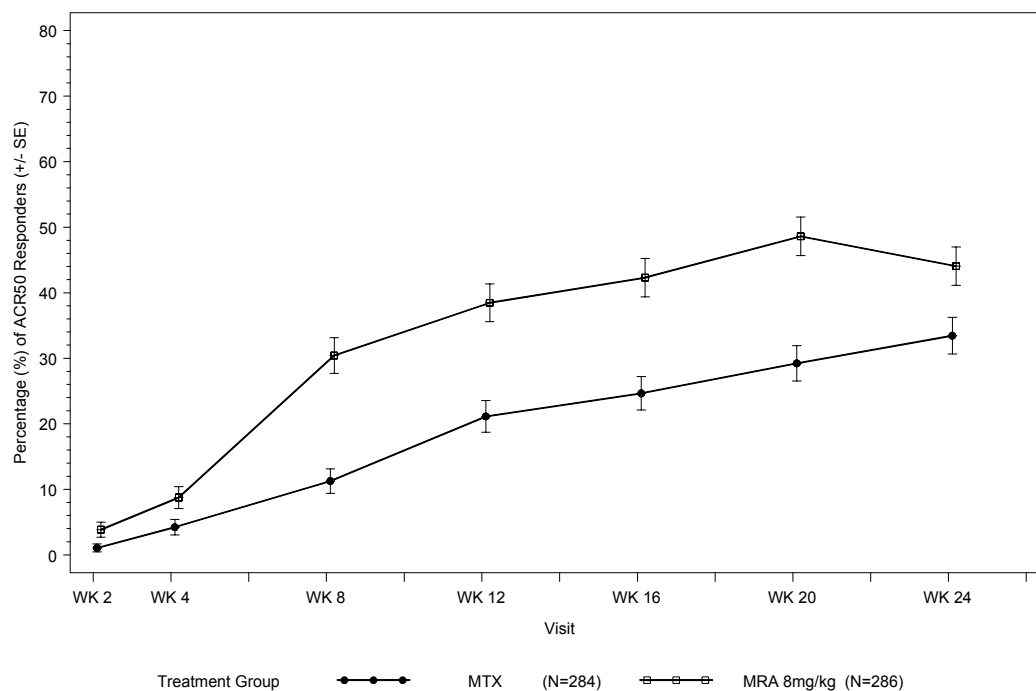


LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Program : \$PROD/wa17824/efpercseacr\_50.sas / Output : \$PROD/cdp11935/j17824a/reports/efpercseacr\_502i.cgm  
24SEP2007 12:06

## Appendix 16 ACR50 Response Rates by Visit – Monotherapy Study

efpercseacr\_505i ACR50 Response Rates by Visit - All Patients excluding Placebo Patients (ITT Population)

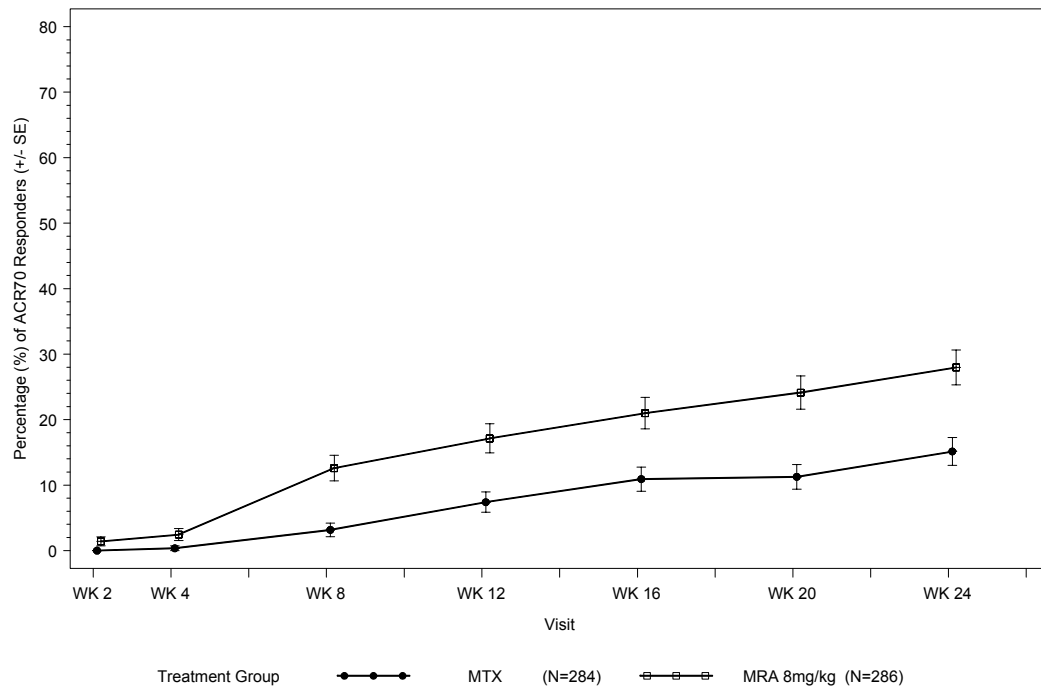


LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Program : \$PROD/wa17824/efpercseacr\_50.sas / Output : \$PROD/cdp11935/j17824a/reports/efpercseacr\_505i.cgm  
24SEP2007 12:06

## Appendix 17 ACR70 Response Rates by Visit – Monotherapy Study

efpercseacr\_507i ACR70 Response Rates by Visit - All Patients excluding Placebo Patients (ITT Population)



LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Program : \$PROD/wa17824/efpercseacr\_50.sas / Output : \$PROD/cdp11935/j17824a/reports/efpercseacr\_507i.cgm  
24SEP2007 12:06

**Appendix 18 Listing of Deaths in Patients Treated with Tocilizumab for Non RA Indications (January 31, 2008)**

Indication	Study	Age / Gender	Cause of Death	Relationship to TCZ	
Systemic Juvenile Idiopathic Arthritis	Compassionate use	5F	Acute myeloid leukemia	No	
	Compassionate use	3F	Juvenile arthritis	No	
	MRA324JP	3F	Histiocytosis hematophagic	Yes	
	MRA324JP	22M	Cardiac amyloidosis	No	
Multiple Myeloma	LRO310	57F	Pneumonia, Cholesystitis, Neurological symptom	No, No, No	
	LRO310	67F	Sepsis	No	
	LRO310	77F	Multiple myeloma	No	
	LRO310	65F	Multiple myeloma	No	
	LRO310	71F	Acute renal failure	No	
	Compassionate use	53M	Multiple myeloma	No	
	Castleman’s Disease	MRA006JP	66M	Chronic myelomonocytic leukemia	No
ML19367		77F	Cholestatic jaundice	No	
ML19367		74F	Gastrointestinal hemorrhage	Yes	
ML19367		72M	Gastric cancer	No	
ML19367		34M	Cerebral hemorrhage	No	
ML19367		46M	Renal failure acute	No	
ML19367		38F	Respiratory failure Castleman’s disease	No	
ML19367		61M	Respiratory failure	No	
ML19367		62F	Cerebral infarction	No	
ML19367		18F	Respiratory failure	No	
ML19367		56M	Pneumonia	No	
ML19367		33F	Hypercapnia	No	
			Chronic respiratory failure	No	
ML19367		57F	Pneumonia	Yes	
ML19367		53F	Gastrointestinal hemorrhage	Yes	
		45M	Pulmonary hemorrhage	No	
Compassionate use		33M	Death	Yes	
Still Disease		Compassionate use	52M	Cardiac failure	Yes
CINCA syndrome		Compassionate use	2M	Cardiac failure congestive	Yes
			Interstitial lung disease	No	
After October 1, 2007 to January 31, 2008					
Castleman’s Disease	ML19367	18F	Respiratory failure	No	
	MRA423JP	41M	Pancreatic cyst	Yes	

## Appendix 19 Malignancy Rates in the RA Population from the Literature

	RR	95% CI	
		Lower	Upper
<b>Lung Cancer</b>			
Moritomo, 1995	0.00	0.00	1.82
Cibere, 1997	1.08	0.61	1.75
Wolfe, 2007	1.20	1.00	1.40
Gridley, 1993	1.31	1.00	1.70
Thomas, 2000	1.39	1.30	1.50
Askling, 2005	1.48	1.33	1.65
Mellemkjaer, 1996	1.50	1.30	1.70
Askling, 2005 (anti-TNF)	1.80	0.90	3.30
Kauppi, 1996	1.80	1.40	2.20
Setoguchi, 2006	1.80	1.52	2.05
Askling, 2005 (Early RA))	2.40	1.50	3.60
Matteson, 1991 (DMARDs)	3.37	1.58	7.34
Abasolo, 2007	3.50	1.40	7.10
<b>Lymphoma</b>			
Geborek, 2005	1.30	0.20	4.50
Wolfe, 2007	1.80	1.50	2.20
Askling, 2005	1.90	1.70	2.10
Gridley, 1993	1.98	1.50	2.60
Askling, 2005 (Early RA)	2.00	1.00	3.50
Ekstrom, 2003	2.00	1.83	2.17
Askling, 2005 (anti-TNF)	2.90	1.30	5.50
Frankling, 2006	2.94	1.34	5.57
Geborek, 2005 (anti-TNF)	11.50	3.70	26.90
<b>Stomach Cancer</b>			
Askling, 2005 (anti-TNF)	0.00	0.00	7.00
Gridley, 1993	0.63	0.50	0.90
Askling, 2005 (Early RA)	0.70	0.08	2.50
Askling, 2005	1.10	0.89	1.33
<b>Cervix Cancer</b>			
Askling, 2005 (Early RA)	0.80	0.02	4.30
Askling, 2005 (anti-TNF)	1.00	0.00	5.80
Askling, 2005	1.03	0.71	1.45
Mellemkjaer, 1996	1.10	0.80	1.50



## Appendix 20 Glossary of Preferred Terms of Infusion Reaction Adverse Events

Basket Name	AE Preferred Term
Infusion reaction (Basket)	<p> ALLERGIC BRONCHITIS  ALLERGIC OEDEMA  ANAPHYLACTIC REACTION  ANAPHYLACTIC SHOCK  ANAPHYLACTOID REACTION  ANAPHYLACTOID SHOCK  ANGIOEDEMA  ARRHYTHMIA  ARRHYTHMIA SUPRAVENTRICULAR  ARTHRALGIA  ASTHMA  ATRIAL FIBRILLATION  BODY TEMPERATURE INCREASED  BRONCHIAL OEDEMA  BRONCHOSPASM  CHILLS  CIRCUMORAL OEDEMA  CONJUNCTIVITIS  COUGH  CYANOSIS  DERMATITIS ALLERGIC  DIZZINESS  DIZZINESS POSTURAL  DRY THROAT  DYSAESTHESIA  DYSAESTHESIA PHARYNX  DYSGEUSIA  DYSPHONIA  DYSPOEA  EAR PRURITUS  ERYTHEMA  ERYTHEMA OF EYELID  EXTRASYSTOLES  EYE IRRITATION  EYE OEDEMA  EYE PRURITUS  EYE SWELLING  EYELID IRRITATION  EYELID OEDEMA  EYELIDS PRURITUS  FACE OEDEMA  FATIGUE  FEELING COLD  FEELING HOT  FLUSHING  GENERALISED ERYTHEMA  GENERALISED OEDEMA  HEADACHE  HOT FLUSH  HYPERSENSITIVITY  HYPERTENSION  HYPERTHERMIA  HYPOTENSION  HYPOXIA  INFLUENZA LIKE ILLNESS  INFUSION RELATED REACTION  LARYNGEAL OEDEMA  LARYNGOSPASM  LARYNGOTRACHEAL OEDEMA  LIP OEDEMA  LIP SWELLING  LOCALISED OEDEMA  MALAISE  MYALGIA  NASAL CONGESTION  NASAL DISCOMFORT  NASAL OEDEMA  OEDEMA  OEDEMA MOUTH </p>

Preferred terms within Infusion Reaction Grouped Term  
Program : \$PROD/cdl19351/p11935b/SLae\_gloss.sas  
Output : \$PROD/cdl19351/p11935b/reports/SLae\_gloss\_ir.r18

## Appendix 20 Glossary of Preferred Terms of Infusion Reaction Adverse Events (Cont.)

Basket Name	AE Preferred Term
	<p> OEDEMA PERIPHERAL  ORAL DISCOMFORT  ORAL DYSAESTHESIA  ORAL PRURITUS  ORBITAL OEDEMA  OROPHARYNGEAL SPASM  OROPHARYNGEAL SWELLING  PAIN  PALLOR  PALPITATIONS  PARAESTHESIA  PARAESTHESIA ORAL  PAROSMIA  PERIORBITAL OEDEMA  PHARYNGEAL OEDEMA  PRESYNCOPE  PRURITUS  PRURITUS ALLERGIC  PRURITUS GENERALISED  PYREXIA  RASH  RASH ERYTHEMATOUS  RASH GENERALISED  RASH MACULAR  RASH PRURITIC  RESPIRATION ABNORMAL  RESPIRATORY TRACT CONGESTION  RHINITIS ALLERGIC  RHINORRHOEA  SINUS BRADYCARDIA  SINUS TACHYCARDIA  SKIN BURNING SENSATION  SKIN DISCOMFORT  SKIN IRRITATION  SKIN OEDEMA  SNEEZING  SUPRAVENTRICULAR EXTRASYSTOLES  SUPRAVENTRICULAR TACHYARRHYTHMIA  SUPRAVENTRICULAR TACHYCARDIA  SWELLING  SWELLING FACE  SWOLLEN TONGUE  SYNCOPE  TACHYARRHYTHMIA  TACHYCARDIA  TACHYPNOEA  THROAT IRRITATION  THROAT TIGHTNESS  TONGUE DISORDER  TONGUE OEDEMA  URTICARIA  VOMITING  WHEEZING </p>
Preferred terms within Infusion Reaction Grouped Term	

## **12. SUPPLEMENTAL REPORT – WP18633**

### **12.1 Background**

Study WP18633 is a multi-center, open-label, randomized, drug interaction study to investigate the pharmacokinetics of simvastatin (a substrate for CYP3A4) and MTX in combination with tocilizumab in RA patients.

Patients were eligible for this study if they met the following inclusion criteria:

- RA for  $\geq 6$  months with a CRP concentration of  $> 1.5$  mg/dL
- Were receiving MTX for  $\geq 12$  weeks immediately prior to Day 1 with a stable dose between 10 and 25 mg/week during the last 8 of 12 weeks
- If on NSAIDs, were receiving a stable regimen 4 weeks prior to Day 1
- If on oral corticosteroids, the dose was  $\leq 10$  mg prednisone or equivalent and was stable for 2 wks prior to Day 1

Eligible patients were randomized into one of two treatment groups. Twelve patients in Group 1 received tocilizumab 10 mg/kg on Day 8, MTX (between 10-25 mg) once weekly, simvastatin (40 mg) on Days 1, 15, and 43 and folic acid ( $\geq 5$  mg/week). Eleven patients in Group 2 received tocilizumab (10 mg/kg) on Day 8, MTX (10-25 mg) once weekly, and folic acid ( $\geq 5$  mg/week).

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

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

Blood samples were drawn immediately after the completion of the infusion of tocilizumab and at 4, 12, and 24 hours after MTX administration on Days 8/9 for the analysis of tocilizumab serum levels and MTX plasma concentrations.

Serum levels of CRP, IL-6, sIL-6R, and other biomarkers were measured throughout the study. Antibodies to tocilizumab were measured at screening and at follow-up. Hepcidin was measured in urine on Days 1, 8 (1, 12, and 14 hours post-dose), 15, 22, and 43. Iron and ferritin were measured in serum on Days 1, 8 (pre-dose and 1, 4, 12, and 24 hours post-dose), 15, 22, and 43.

Follow-up procedures, including physical examination, ECG, vital signs, and clinical laboratory tests, were performed 8 weeks after tocilizumab infusion.

### **12.2 Results**

#### **12.2.1 Pharmacodynamic Results**

Simvastatin did not affect the pharmacodynamics of tocilizumab, as no significant differences in pharmacodynamic markers were observed between the two treatment groups. Following a tocilizumab infusion of 10 mg/kg, mean serum IL-6 concentrations

rose immediately and peak concentrations were observed between one and eight days post dose. Similar findings were observed with sIL-6R. Approximately 8 weeks after tocilizumab administration, these two markers had nearly returned to their baseline values. Serum concentrations of CRP were elevated at baseline with mean levels of approximately 35 mg/L, as expected from patients with active RA. Following tocilizumab administration, CRP concentrations were reduced to normal within 1 week after infusion and remained within normal limits for about 4 weeks. An initial increase of urinary excretion of hepcidin occurred 1 hour after tocilizumab infusion and was immediately followed by decreased excretion.

### **12.2.2 Pharmacokinetic Results**

Plasma concentrations of simvastatin were higher in RA patients prior to tocilizumab administration than those reported for healthy volunteers. Tocilizumab reduced significantly the  $AUC_{last}$  and  $C_{max}$  of simvastatin on Day 15 (1 week after tocilizumab infusion) and Day 43 (5 weeks after tocilizumab infusion). Similar findings were observed for simvastatin acid, the main metabolite. The AUC of simvastatin acid was reduced by ~40% on Day 15 and by ~20% on Day 43 compared to Day 1.

### **12.2.3 Safety Results**

In both treatment groups, 17 of 23 patients reported at least one adverse event. Most adverse events were mild to moderate in intensity and were reported as unrelated to treatment by the investigator. No deaths or serious adverse events were encountered in this study. Within 24 hours of finishing the infusion, one patient had two infusion-associated adverse events (chills and myalgia) that were mild to moderate. This patient did not have the study medication dose modified/interrupted. The patient also did not withdraw from treatment because of these infusion-associated events.

### **12.2.4 Conclusions**

Administration of tocilizumab in RA patients significantly reduced the exposure to simvastatin to levels close to those found in non-RA patients. This effect persisted for 5 weeks after tocilizumab administration. In addition, tocilizumab had no relevant effect on MTX exposure.

Based on the decrease in mean CRP and mean neutrophil count, tocilizumab demonstrated a rapid blockade of IL-6 signaling, which persisted for several weeks after tocilizumab administration.

A single dose of 10 mg/kg of tocilizumab in addition to MTX once weekly, with or without single doses of simvastatin, were well tolerated in this study with no unexpected safety findings observed.

## **13. SUPPLEMENTAL REPORT – WA17823**

### **13.1 Background**

Study WA17823 (LITHE) is a two year phase III, 3-arm randomized, double-blind, placebo-controlled, parallel group, international, multi-center study in patients with moderate to severe, active RA who have had an inadequate response to MTX. The study was designed to assess safety, reduction in signs and symptoms of RA after 6 months, prevention of joint damage at one year (with confirmation at two years), and improvement in physical function at one year (with confirmation at two years) of tocilizumab therapy in combination with MTX versus MTX alone. Data from an interim analysis of 24-week data demonstrating the safety and efficacy of tocilizumab in reducing the signs and symptoms of RA were reported previously in BLA 125276/0.

The primary objectives at year one of the study were the assessment of the efficacy of tocilizumab versus placebo, in combination with MTX, with regard to prevention of structural joint damage and improvement in physical function.

Patients were eligible for this study if they had moderate to severe, active RA, (defined as having at least 6 swollen and at least 8 tender joints, either CRP  $\geq$  1mg/dL or an ESR of  $\geq$  28mm, and at least one joint in the wrist, hand or feet (with the exception of the distal phalangeal joints of the hand) with a radiographically demonstrated erosion), despite at least 12 weeks prior therapy with MTX and were being treated on an outpatient basis. Patients were excluded from the study if they had responded inadequately to prior therapy with a biologic treatment, but were permitted entry into the study if they had terminated treatment due to cost or discomfort with the subcutaneous injections.

Eligible patients were randomized on a 1:1:1 basis to one of the following treatment groups: 4 mg/kg tocilizumab, 8 mg/kg tocilizumab or placebo intravenously (IV) every 4 weeks in combination with 10 to 25 mg MTX weekly. All patients received a stable dose of at least 5 mg folate (or equivalent) weekly. In addition, stable oral NSAID and oral corticosteroid ( $\leq$  10 mg/day prednisone equivalent) doses were allowed and continued unchanged for the initial 24 weeks of the study.

Patients received an infusion of tocilizumab or tocilizumab-placebo in a blinded fashion, every 4 weeks for one year, followed by open-label treatment with 8 mg/kg tocilizumab infusions every 4 weeks for the second year. Only patients achieving a  $\geq$  70% improvement from baseline in swollen joint count (SJC) and tender joint count (TJC) at 2 consecutive visits were allowed to continue on randomized study therapy into year 2 in a blinded fashion.

Escape therapy with tocilizumab was permitted for patients who had reached week 16 (or later) of the study and had achieved less than a 20% improvement from baseline in both SJC and TJC. Tocilizumab escape therapy dosing occurred in a stepwise fashion as shown in [Table 47](#) and remained double-blind through step 1 but was open-label for patients entering step 2 escape therapy.

**Table 47**      **Stepwise Tocilizumab Escape Therapy**

<b>Randomized Treatment (for ≥ 16 weeks)</b>	<b>1st step Tocilizumab Escape (for ≥ 12 weeks duration)</b>	<b>2nd step Tocilizumab Escape (for ≥ 12 weeks duration)</b>
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

Radiographs were scored using the Genant modification of the Sharp scoring system at a central reading facility (Synarc, Inc, San Francisco, California) by two independent expert readers. These readers were blinded to the treatment group assignment, the chronologic order of the radiographs and the patients' clinical response.

## **13.2 Results**

### **13.2.1 Study Population and Disposition of Patients**

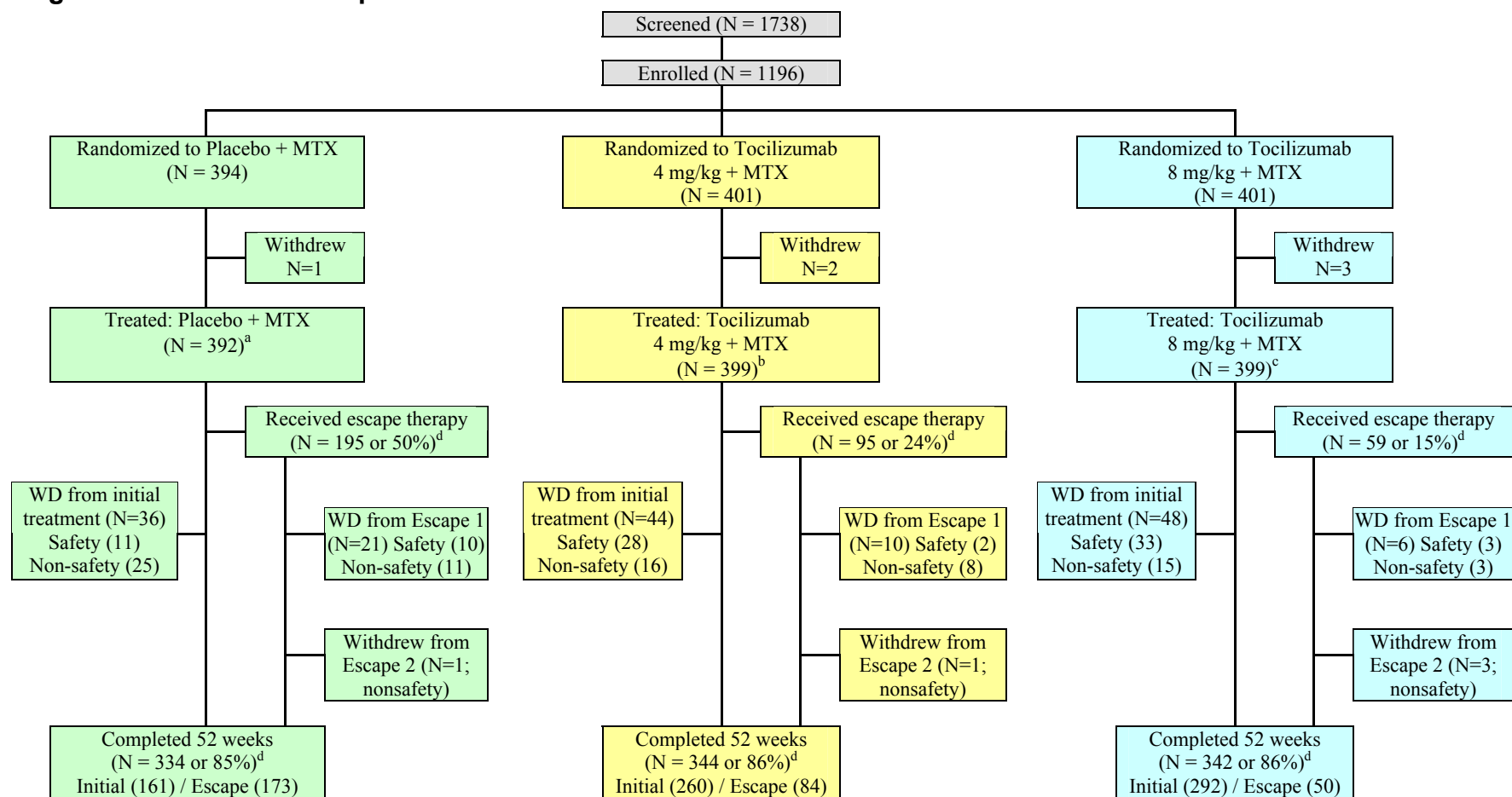
A total of 1783 patients were screened for the study and 1196 patients were enrolled. Of the 1196 patients enrolled into the study, 394 were randomized to the placebo + MTX group and 401 patients into each of the tocilizumab + MTX groups ([Figure 20](#)). Six patients (1 placebo + MTX, 2 tocilizumab 4 mg/kg + MTX, 3 tocilizumab 8 mg/kg + MTX) did not receive any study medication.

A total of 349 (29%) of the 1190 treated patients received escape therapy, more from the placebo + MTX group (195 patients [50%]) compared with the 4 and 8 mg/kg tocilizumab + MTX groups (95 [24%] and 59 [15%], respectively, [Figure 20](#)). Of the 349 patients who received escape therapy, 75% entered escape during the first 6 months of the study; 50 of these patients went on to receive escape 2 therapy.

The proportion of patients reaching week 52 on their initial randomized study treatment was 41% in the placebo + MTX group compared with 65% and 73% in the tocilizumab 4 mg/kg + MTX and tocilizumab 8 mg/kg + MTX groups, respectively.

Baseline and at least one post baseline radiographs were received for over 90% of the study population in all treatment groups and a week 52 post baseline radiograph was obtained in 82-89% of patients.

**Figure 20 Patient Disposition**



a) excludes one patient randomized to placebo + MTX who received tocilizumab 4 mg/kg + MTX; b) includes one patient randomized to placebo + MTX but received tocilizumab 4 mg/kg + MTX and excludes one patient who received tocilizumab 8 mg/kg + MTX; c) includes one patient randomized to tocilizumab 4 mg/kg + MTX but received tocilizumab 8 mg/kg + MTX; d) Percentages based on the number of treated patients. WD = Withdrew.

Sources: stex11\_in, stex11\_esc1, stex11\_esc2, sle01\_esc.

### 13.2.1.1 Patients Withdrawn Prematurely from Treatment

A total of 128 patients (36 [9%] in the placebo vs 44 [11%] and 48 [12%] in the 4 mg/kg and 8 mg/kg tocilizumab + MTX groups) withdrew prematurely from initial study treatment (Table 48).

Premature withdrawal from initial treatment due to lack of therapeutic response was more frequently observed in the placebo + MTX group (12 patients) than in either tocilizumab + MTX group (1 and 2 patients, respectively). As receipt of escape therapy could also be considered to demonstrate inadequate therapeutic response, notably more patients in the placebo + MTX group (50%) compared with the tocilizumab + MTX groups (24% and 15%, respectively) stopped initial therapy for this reason.

**Table 48 Summary of Patients Withdrawn from Initial Therapy (All Randomized)**

stex11\_in Summary of Patients Withdrawn from Trial Treatment on Initial Treatment by Trial Treatment (All Patients)  
Protocol(s): J17823E  
Analysis: ALL PATIENTS Center: ALL CENTERS

Reason for Withdrawal	PLACEBO + MTX N = 392 No. (%)	MRA 4 MG/KG + MTX N = 399 No. (%)	MRA 8 MG/KG + MTX N = 399 No. (%)
Safety	11 ( 3)	28 ( 7)	33 ( 8)
Adverse Event(a)	10	28	30
Death	1	0	3
Non-Safety	25 ( 6)	16 ( 4)	15 ( 4)
Insufficient Therapeutic Response	12	1	2
Violation of Selection Criteria at Entry	1	0	0
Refused Treatment(b)	10	10	12
Failure to Return	1	3	0
Other	1	2	1
Total	36 ( 9)	44 ( 11)	48 ( 12)

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'

Percentages are based on N.

One patient who was randomized to the Placebo + MTX group but withdrew before first infusion is not included in this output

Two patients who were randomized to the MRA 4 mg/kg + MTX group but withdrew before first infusion are not included in this output

Three patients who were randomized to the MRA 8 mg/kg + MTX group but withdrew before first infusion are not included in this output

EX11 18APR2008:10:46:34

Of the 349 patients who received escape therapy with tocilizumab, 42 patients prematurely stopped study treatment (Table 49).



**Table 49      Summary of Patients Withdrawn from Escape Therapy (All Randomized)**

Protocol(s): J17823E

Analysis: ALL PATIENTS

Center: ALL CENTERS

Reason for Withdrawal	MTX to MRA 4mg/kg escape  N = 165 No. (%)	MTX to MRA 4mg/kg escape to MRA 8mg/kg escape N = 30 No. (%)	MRA 4mg/kg to MRA 8mg/kg escape N = 95 No. (%)	MRA 8mg/kg to MRA 8mg/kg escape N = 59 No. (%)
Safety	10 ( 6)	0 ( 0)	2 ( 2)	3 ( 5)
Adverse Event(a)	9	0	2	2
Death	1	0	0	1
Non-Safety	11 ( 7)	1 ( 3)	9 ( 10)	6 ( 10)
Insufficient Therapeutic Response	5	0	3	3
Refused Treatment(b)	4	1	5	2
Failure to Return	2	0	0	1
Other	0	0	1	0
Total	21 ( 13)	1 ( 3)	11 ( 12)	8 ( 14)

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'

Percentages are based on N.

EX11 20APR2008:12:24:41

Sources: stex11\_esc1 and stex11\_esc2 PDRD

### 13.2.1.2 Demographic Data and Baseline Characteristics

The treatment groups were balanced for the demographic characteristics (gender, age, height, weight, race and family history of coronary heart disease), to the ACR characteristics (number of active joints, functional status, mean and median acute phase reactant (CRP and ESR) at baseline, patient and physicians assessment of global disease status and patient pain rating) and RA characteristics (duration of RA, number of previous DMARDS/anti-TNFs, baseline rheumatoid factor, baseline DAS28, oral steroid use and baseline MTX dose) (Table 50).

**Table 50 Summary of Baseline Demographic, ACR and RA baseline Characteristics (ITT Population)**

	PLACEBO + MTX N = 393	MRA 4MG/KG + MTX N = 399	MRA 8MG/KG + MTX N = 398
Sex			
MALE	65 ( 17%)	63 ( 16%)	73 ( 18%)
FEMALE	328 ( 83%)	336 ( 84%)	325 ( 82%)
Age in years			
Mean	51.3	51.4	53.4
SD	12.41	12.59	11.72
Height in cm			
Mean	162.1	162.3	162.0
SD	8.71	8.20	9.06
Weight in kg			
Mean	73.8	73.2	72.1
SD	20.27	17.96	16.88
Race Category			
AMERICAN INDIAN OR ALASKA NATIVE	15 ( 4%)	19 ( 5%)	13 ( 3%)
ASIAN	22 ( 6%)	20 ( 5%)	26 ( 7%)
BLACK	16 ( 4%)	23 ( 6%)	21 ( 5%)
OTHER	62 ( 16%)	57 ( 14%)	58 ( 15%)
WHITE	278 ( 71%)	280 ( 70%)	280 ( 70%)
Ethnicity			
HISPANIC	142 ( 36%)	137 ( 34%)	138 ( 35%)
NON-HISPANIC	251 ( 64%)	262 ( 66%)	260 ( 65%)
n	393	399	398
Reproductive Status			
3/4	-	-	1 ( <1%)
N/A	1 ( <1%)	-	-
NA	1 ( <1%)	2 ( <1%)	-
POSTMENOPAUSAL	158 ( 48%)	154 ( 46%)	185 ( 57%)
SURGICALLY STERIL.	69 ( 21%)	74 ( 22%)	75 ( 23%)
WITH CONT. PROT.	100 ( 30%)	108 ( 32%)	64 ( 20%)
Does the Patient Smoke?			
NO	332 ( 84%)	333 ( 83%)	323 ( 81%)
YES	61 ( 16%)	66 ( 17%)	75 ( 19%)
Family History of Coronary Heart Disease			
NO	340 ( 87%)	347 ( 87%)	348 ( 87%)
YES	53 ( 13%)	52 ( 13%)	50 ( 13%)

n represents number of patients contributing to summary statistics.  
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.  
For reproductive status, NA stands for Not Applicable  
For reproductive status, Cont. Prot. means Contraceptive Protection  
DM11 20APR2008:17:10:33 (PDRD)

**Table 50 Summary of Baseline Demographic, ACR and RA baseline Characteristics (ITT Population) (Cont.)**

	PLACEBO + MTX N = 393	MRA 4MG/KG + MTX N = 399	MRA 8MG/KG + MTX N = 398
Duration of RA (years)			
Mean	8.96	9.43	9.29
SD	8.074	7.867	8.209
Number of Previous DMARDs/ Anti-TNFs			
Mean	1.6	1.7	1.6
SD	1.49	1.44	1.43
Baseline Rheumatoid Factor			
NEGATIVE	72 ( 18%)	77 ( 19%)	68 ( 17%)
POSITIVE	321 ( 82%)	322 ( 81%)	330 ( 83%)
Baseline DAS28			
Mean	6.533	6.508	6.553
SD	0.9590	0.9406	0.9596
Oral Steroid Use			
NO	119 ( 30%)	124 ( 31%)	151 ( 38%)
YES	274 ( 70%)	275 ( 69%)	247 ( 62%)
Baseline MTX dose mg/week			
Mean	15.0	15.0	15.4
SD	4.23	4.27	10.60
Tender Joint Count			
Mean	27.9	27.9	29.3
SD	14.80	14.15	15.22
Swollen Joint Count			
Mean	16.6	17.0	17.3
SD	9.23	9.78	9.48
ESR mm/hr			
Mean	46.5	45.9	46.4
SD	24.69	25.12	24.80
CRP mg/dL			
Mean	2.235	2.076	2.333
SD	2.5068	2.3892	2.6067
HAQ			
Mean	1.5	1.5	1.5
SD	0.62	0.64	0.60
Pain VAS (100mm)			
Mean	55.3	53.3	55.7
SD	22.07	21.97	22.34
Patient VAS (100mm)			
Mean	63.1	61.0	62.7
SD	23.36	23.25	22.49
Physician VAS (100mm)			
Mean	63.1	62.3	62.7
SD	17.34	16.80	16.90

n represents number of patients contributing to summary statistics.  
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.  
DM11 20APR2008:17:10:05 (PDRD)

Source outputs: stdm11\_gen\_itt, stdm11\_ra\_itt, stdm11\_acr\_itt.

There were no relevant differences between the treatment groups with respect to the incidence and types of previous treatments for RA. Between 11% and 12% of patients had previously received anti-TNF therapy (specifically etanercept, infliximab or adalimumab) with the majority of these patients receiving one agent previously.

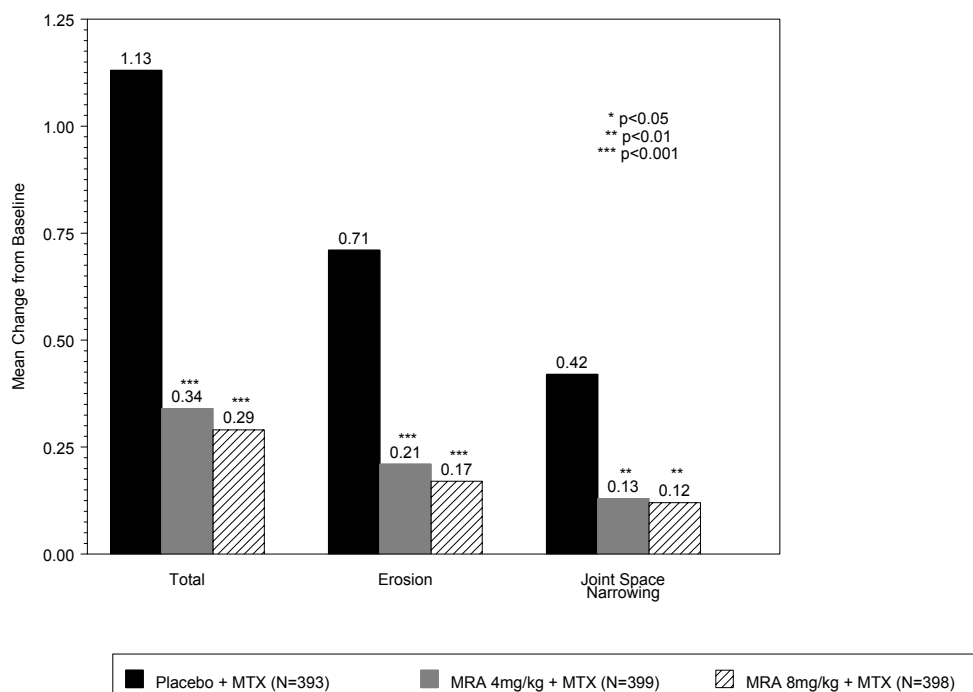
## 13.2.2 Radiographic Scores

### 13.2.2.1 Overview

Mean changes from baseline in radiographic scores (total Sharp-Genant, erosion, and JSN) at week 52 were all statistically significantly lower, indicating a favorable response in the tocilizumab + MTX groups compared with the placebo + MTX group (Figure 2).

**Figure 21 Mean Change from Baseline in Radiographic Scores at Week 52 — Linear Extrapolation Method (ITT Population)**

ef\_xraybarmncradsc Mean Change from Baseline in Radiographic Scores at Week 52 (Campaign 1) - Linear Extrapolation Method (ITT Population)



Data collected after withdrawal or on escape therapy is excluded. Missing week 52 x-ray data is imputed using linear extrapolation. All comparisons are to Placebo+MTX using Van Elteren's test stratified by region. Campaign 1 consists of the evaluations of Baseline, Week 24, Week 52, early withdrawal or escape therapy readings taken up to the Week 52 visit.

Program : \$PROD/cd11935t/j17823e/ef\_xraybar.sas  
Output : \$PROD/cd11935t/j17823e/reports/ef\_xraybarmncradsc.cgm  
30APR2008 16:32

### 13.2.2.2 Primary Efficacy: Change from Baseline in Total Sharp-Genant Score at Week 52

The primary radiographic endpoint was the change from baseline in the total Sharp-Genant score at week 52. The mean change was significantly lower for patients treated with tocilizumab + MTX (0.34 and 0.29 for the 4 and 8 mg/kg groups, respectively) than for patients who received placebo + MTX (1.13,  $p < 0.0001$  for both comparisons, Table 10).

**Table 51 Summary and Analysis of Change from Baseline in Total Sharp-Genant Score at Week 52 — Linear Extrapolation Method (ITT Population)**

et\_xraychb1 Summary and Analysis of Change from Baseline in Total Sharp-Genant Score at Week 52 (Campaign 1) - Linear Extrapolation Method (ITT Population)

Visit	Placebo + MTX (N=393)	MRA 4mg/kg + MTX (N=399)	MRA 8mg/kg + MTX (N=398)
Baseline			
n	290	339	348
Mean	28.79	29.54	29.08
SD	32.426	28.700	28.504
Median	17.68	21.35	21.40
Min-Max	0.0-190.5	0.0-171.4	0.0-178.7
Week 52			
n	290	339	348
Mean	29.91	29.88	29.37
SD	32.376	28.768	28.544
Median	20.19	21.49	21.40
Min-Max	0.0-192.5	0.0-171.4	0.0-178.7
Change from baseline at Week 52			
n	290	339	348
Mean	1.13	0.34	0.29
SD	2.962	1.451	1.282
Median	0.00	0.00	0.00
Min-Max	-8.8-20.1	-6.4-14.2	-5.7-7.5
P-value (a)		<0.0001	<0.0001

(a) All comparisons are to Placebo+MTX using Van Elteren's test stratified by region. Since the radiographic score is tested at both 52 and 104 weeks, the nominal overall significance level at each time point is set to 0.025. Data collected after withdrawal or on escape therapy is excluded.

Missing Week 52 data is imputed using linear extrapolation.

Campaign 1 consists of the evaluations of Baseline, Week 24, Week 52, early withdrawal or escape therapy readings taken up to the Week 52 visit.

Program : \$PROD/cdl1935t/j17823e/et\_xraychb.sas

Output : \$PROD/cdl1935t/j17823e/reports/et\_xraychb1.rp8 25APR2008 17 :45

Results of the sensitivity and subgroup analyses were consistent with those obtained by the primary analysis.

### 13.2.2.3 Change from Baseline in Total Sharp-Genant Scores at Week 24

The mean change from baseline in total Sharp-Genant score at week 24 (observed case analysis) was significantly lower for patients treated with tocilizumab + MTX (0.22 and 0.19 for the 4 and 8 mg/kg groups, respectively) than for patients who received placebo + MTX (0.51,  $p=0.0038$  and  $p<0.0001$ , respectively).

The change from baseline in total Sharp-Genant score worsened between week 24 and week 52 in the placebo + MTX group, but remained stable between the 2 timepoints in the tocilizumab + MTX groups.

### 13.2.2.4 Change from Baseline in Erosion Score

At week 52, the mean change from baseline in the total erosion score (linear extrapolation method) was significantly lower for patients treated with tocilizumab + MTX (0.21 and 0.17 for the 4 mg/kg and 8 mg/kg groups, respectively) than for patients who received placebo + MTX (0.71,  $p=0.0001$  and  $p<0.0001$ , respectively).

Results of the sensitivity analyses were consistent with those obtained by the primary analysis.

### 13.2.2.5 *Change from Baseline in Joint Space Narrowing Scores*

At week 52, the mean change from baseline in the JSN score (linear extrapolation method) was significantly lower for patients treated with tocilizumab + MTX (0.13 and 0.12 for the 4 mg/kg and 8 mg/kg groups, respectively) than for patients who received placebo + MTX (0.42,  $p=0.0086$  and  $0.0042$ , respectively).

Results of the sensitivity analyses for change from baseline in JSN score at week 52 were consistent with those obtained by the primary analysis.

### 13.2.2.6 *Proportion of Patients Without Progression of Total Sharp-Genant Score*

At week 52 the proportion of patients with no progression (ie, no worsening) from baseline in their total Sharp-Genant score was greater in the tocilizumab + MTX groups (81% and 85% in the 4 mg/kg and 8 mg/kg groups, respectively) compared to the placebo + MTX group (67%). The differences between both tocilizumab + MTX groups and placebo + MTX were statistically significant in the logistic regression analysis ( $p=0.0001$  and  $p<0.0001$  for 4 and 8 mg/kg group vs placebo, respectively).

**Table 52**      **Proportion of Patients with No Progression in Total Sharp-Genant Score — Linear Extrapolation Method (ITT Population)**

et\_xrayprop1 Proportion of Patients With No Progression of Total Sharp-Genant Score at Week 52 (Campaign 1) - Linear Extrapolation Method (ITT Population)

Visit	Placebo + MTX (N=393)	MRA 4mg/kg + MTX (N=399)	MRA 8mg/kg + MTX (N=398)
Week 52			
n	290	339	348
No Progression	195 (67.2%)	273 (80.5%)	294 (84.5%)

No progression of Total Sharp-Genant score is defined as a change from baseline of less than or equal to zero. Data collected after withdrawal or on escape therapy is excluded. Missing week 52 x-ray data is imputed using linear extrapolation. Campaign 1 consists of the evaluations of Baseline, Week 24, Week 52, early withdrawal or escape therapy readings taken up to the Week 52 visit.  
Program : \$PROD/cdl1935t/j17823e/et\_xrayprop.sas  
Output : \$PROD/cdl1935t/j17823e/reports/et\_xrayprop1.rp8 29APR2008 10:48

### 13.2.2.7 *Proportion of Patients With No Progression of Erosion and Joint Space Narrowing Scores*

At week 52, the proportion of patients with no erosive progression from baseline was greater in the tocilizumab + MTX groups (83% and 87% in the 4 mg/kg and 8 mg/kg groups, respectively) than in the placebo + MTX group (70%). The differences between both tocilizumab + MTX groups and placebo + MTX were statistically significant in the logistic regression analysis ( $p=0.0002$  and  $<0.0001$  for 4 mg/kg and 8 mg/kg groups vs placebo, respectively).

At week 52, the proportion of patients with no JSN score progression from baseline was greater in the tocilizumab + MTX groups (91% in both groups) than in the

placebo + MTX group (85%). The differences between both tocilizumab + MTX groups and placebo + MTX were statistically significant in the logistic regression analysis ( $p = 0.0195$  and  $0.0237$  for the 4 mg/kg and 8 mg/kg groups vs placebo, respectively).

### 13.2.3 Change in Physical Function as Measured by the AUC for Change from Baseline in HAQ-DI

A co-primary endpoint was the AUC for change from baseline in HAQ-DI up to week 52. ANOVA analysis of the difference in adjusted mean change from baseline for AUC of HAQ-DI showed a significantly greater decrease in both tocilizumab + MTX groups compared with the placebo + MTX group ( $p < 0.0001$  for both comparisons), indicating improved physical function over 12 months with tocilizumab (Table 53). The greatest treatment effect was observed with the 8 mg/kg dose.

**Table 53 ANOVA of the AUC of the Change from Baseline in HAQ-DI Score up to Week 52 (ITT Population)**

etanvarauchaqwk52i Analysis of Variance of the AUC of the Change from Baseline in Health Assessment Questionnaire Disability Index Score up to Week 52 (ITT Population)

	Placebo + MTX (N=393)	MRA 4mg/kg + MTX (N=399)	MRA 8mg/kg + MTX (N=398)
n	366	376	374
Adjusted Mean	-58.11	-128.37	-144.06
Difference		-70.26	-85.95
97.5% CI for difference		(-96.96, -43.56)	(-112.69, -59.22)
p-value		<0.0001	<0.0001

All comparisons are to Placebo + MTX. Analysis adjusted for region. Since physical function is tested at both 52 and 104 weeks, the nominal overall significance level at each time point is set to 0.025.

No imputation used for missing HAQ scores. All assessments are set to missing from the time a patient receives escape therapy, prior to the calculation of the AUC. Where the last observed HAQ score is prior to Week 52, the AUC is standardized to 52 weeks.

Program : \$PROD/cd11935t/etanvarauchaq.sas

Output : \$PROD/cd11935t/j17823e/reports/etanvarauchaqwk52i.rp8 07MAY2008 16:37

The sensitivity analyses confirmed the results seen with the primary analysis.

### 13.2.4 Major Clinical Response

Major clinical response is defined as reaching and sustaining an ACR70 or better response for at least 6 months. The percentage of patients who achieved a major clinical response by week 52 was higher in both tocilizumab groups (4.0% and 6.5% in the 4 mg/kg and 8 mg/kg groups, respectively) compared with placebo (0.5%, Table 54)

**Table 54 Proportions of Patients Achieving a Major Clinical Response by Week 52**

etsumanalmcri Summary and Analysis of the Percentage of Patients who Achieve a Major Clinical Response by Week 52 (ITT Population)

	Placebo + MTX (N=393)	MRA 4mg/kg + MTX (N=399)	MRA 8mg/kg + MTX (N=398)
n	393	399	398
Responders	2 (0.5%)	16 (4.0%)	26 (6.5%)
p-value		0.0010	<.0001

Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons are to placebo + MTX.  
Major Clinical Response is defined as maintaining an ACR70 for 24 weeks or more.  
LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP was used primarily for the calculation of the ACR response, if missing, ESR is substituted. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non-Responder'. Analysis stratified by region.  
Program : \$PROD/cd11935t/etsumanalmcrr.sas  
Output : \$PROD/cd11935t/j17823e/reports/etsumanalmcrr.rp8 06MAY2008 12:45

## 13.2.5 Safety

### 13.2.5.1 Overview of Adverse Events

An overview of adverse events during initial therapy and during escape therapy up to week 52 is provided in [Table 55](#) and [Table 56](#), respectively. A summary of adverse events that were reported in  $\geq 3\%$  of patients during initial randomized therapy is provided in [Table 57](#). The types of adverse events, and the frequency with which they occurred in patients during escape therapy were similar to those reported in patients during initial randomized therapy.

As a consequence of the clinical data cut rule agreed and implemented prior to the database lock, 4 patients who experienced AEs that led to withdrawal on the day of the data cut were not included in the summary table ([Table 56](#)). However, these patients are presented in the disposition tables and are included in withdrawals due to safety reasons. The events that led to withdrawal of initial trial treatment in these 4 patients included: 1 patient with breast cancer in the placebo + MTX group; 1 patient with vasculitis in the tocilizumab 4 mg/kg + MTX group; and 2 patients with elevated transaminases in the tocilizumab 8 mg/kg + MTX group. With the inclusion of these 4 patients, the percentages of patients who experienced AEs that led to withdrawal are 7.3% and 8.5% of patients in the tocilizumab + MTX groups (4 mg/kg and 8 mg/kg, respectively), and 2.6% of patients in the placebo + MTX group.



**Table 55 Overview of Adverse Events During Initial Randomized Therapy (Safety Population)**

	Placebo + MTX (N = 392)		Tocilizumab 4 mg/kg + MTX (N = 399)		Tocilizumab 8 mg/kg + MTX (N = 399)	
<b>Adverse Events</b>						
Any AEs	252	(64%)	310	(78%)	310	(78%)
Any Severe AEs <sup>a</sup>	33	(8%)	56	(14%)	51	(13%)
And SAEs	22	(6%)	35	(9%)	34	(9%)
AEs related to treatment <sup>b</sup>	156	(40%)	201	(50%)	221	(55%)
SAEs related to treatment	8	(2%)	13	(3%)	15	(4%)
AEs leading to withdrawal	9	(2%)	28	(7%)	32	(8%)
AEs leading to dose interruption	42	(11%)	75	(19%)	88	(22%)
Deaths	1	(<1%)	—	—	3	(<1%)

Sources: stae11\_1; stae11\_2; stae17; stae11\_r; stae11\_r\_s; stae11\_wd; stae11\_dmod; stdd11.

<sup>a</sup>Intensity of AEs were graded as mild, moderate, or severe.

<sup>b</sup>Related = remote, possible, or probable relationship to study treatment (investigator assessment).

**Table 56 Overview of Adverse Events During Escape Therapy (Safety Population)**

	Placebo to Tocilizumab 4 mg/kg + MTX (N = 165)		Placebo to Tocilizumab 4 mg/kg to Tocilizumab 8 mg/kg + MTX (N = 30)		Tocilizumab 4 mg/kg to Tocilizumab 8 mg/kg + MTX (N = 95)		Tocilizumab 8 mg/kg to Tocilizumab 8 mg/kg + MTX (N = 59)	
<b>Adverse Events</b>								
Any AEs	88	(53%)	28	(93%)	74	(78%)	37	(63%)
Any SAEs	12	(7%)	–	–	4	(4%)	4	(7%)
AEs related to treatment <sup>a</sup>	53	(32%)	20	(67%)	55	(58%)	23	(39%)
SAEs related to treatment	7	(4%)	–	–	2	(2%)	1	(2%)
AEs leading to withdrawal	9	(6%)	–	–	2	(2%)	2	(3%)
AEs leading to dose interruption	18	(11%)	3	(10%)	18	(19%)	7	(12%)
Deaths	1	(<1%)	–	–	–	–	1	(<1%)

Sources: stae11\_esc; stae11\_s\_esc; stae11\_r\_esc; stae11\_sr\_esc; stae11\_wd\_esc; stae11\_dm\_esc.

<sup>a</sup>Related = remote, possible, or probable relationship to study treatment (investigator assessment).

**Table 57 Summary of Adverse Events Reported in  $\geq 3$  % of Patients During Initial Randomized Therapy (Safety Population)**

stael3\_3 Summary of Adverse Events With Incidence Rates of At Least 3 % by Trial Treatment (Safety Population) Protocol(s): J17823E  
Analysis: SAFETY Center: ALL CENTERS  
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Adverse Event	PLACEBO + MTX	MRA 4 MG/KG + MTX	MRA 8 MG/KG + MTX
	N = 392 No. (%)	N = 399 No. (%)	N = 399 No. (%)
UPPER RESPIRATORY TRACT INFECTION	26 ( 6.6)	36 ( 9.0)	46 ( 11.5)
URINARY TRACT INFECTION	21 ( 5.4)	21 ( 5.3)	20 ( 5.0)
NASOPHARYNGITIS	16 ( 4.1)	17 ( 4.3)	28 ( 7.0)
HYPERTENSION	12 ( 3.1)	23 ( 5.8)	23 ( 5.8)
BRONCHITIS	16 ( 4.1)	19 ( 4.8)	17 ( 4.3)
TRANSAMINASES INCREASED	6 ( 1.5)	20 ( 5.0)	23 ( 5.8)
INFLUENZA	16 ( 4.1)	16 ( 4.0)	16 ( 4.0)
HEADACHE	8 ( 2.0)	20 ( 5.0)	18 ( 4.5)
SINUSITIS	9 ( 2.3)	22 ( 5.5)	14 ( 3.5)
NAUSEA	15 ( 3.8)	12 ( 3.0)	12 ( 3.0)
BACK PAIN	8 ( 2.0)	15 ( 3.8)	15 ( 3.8)
DIARRHOEA	8 ( 2.0)	16 ( 4.0)	14 ( 3.5)
PHARYNGITIS	9 ( 2.3)	15 ( 3.8)	14 ( 3.5)
ALANINE AMINOTRANSFERASE INCREASED	6 ( 1.5)	6 ( 1.5)	21 ( 5.3)
COUGH	11 ( 2.8)	9 ( 2.3)	13 ( 3.3)
GASTROENTERITIS	9 ( 2.3)	12 ( 3.0)	7 ( 1.8)
RASH	4 ( 1.0)	12 ( 3.0)	11 ( 2.8)
ARTHRALGIA	7 ( 1.8)	7 ( 1.8)	12 ( 3.0)
OEDEMA PERIPHERAL	7 ( 1.8)	5 ( 1.3)	13 ( 3.3)
HYPERCHOLESTEROLAEMIA	4 ( 1.0)	4 ( 1.0)	12 ( 3.0)

Percentages are based on N.

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

Events on escape therapy are excluded

Incidence rate is checked within each individual treatment group

AE13 17APR2008:10:31:23

(1 of 1)

### 13.2.5.2 Deaths

Six deaths were reported in 4 patients during initial randomized therapy and in 2 patients during escape therapy (Table 58).

**Table 58 Listing of Patient Deaths (Safety Population)**

CRTN/Pt. No. Age/Gender	Cause of Death	Day of Death	Relation to Trial Treatment
<b>Placebo + MTX</b>			
46666/2928 63/F	Pulmonary embolism	182	Possible
46732/1544 (Escape 1) 55/F	Wegener's granulomatosis	103	Unrelated
<b>Tocilizumab 8 mg/kg + MTX</b>			
46704/1463 (Escape 1) 57/F	Cerebral hemorrhage	280	Unrelated
46719/2293 73/F	Gastrointestinal infection	324	Possible
46747/1269 62/F	Bronchopneumonia	275	Unrelated
46773/1628 54/F	Sepsis	284	Unrelated

### 13.2.5.3 Serious Adverse Events

A summary of serious adverse events that were reported in  $\geq 2$  patients per tocilizumab treatment group is provided in Table 59. During tocilizumab 4 mg/kg + MTX escape therapy, 3 patients experienced anaphylactic shock/reactions.

**Table 59 Summary of Serious Adverse Events in  $\geq 2$  Patients in Tocilizumab Treatment Groups During Initial Randomized Therapy**

stae11\_2 Summary of Serious Adverse Events by Body System, Preferred Term and Trial Treatment (Safety Population)  
 Serious Adverse Events  
 Protocol(s): J17823E  
 Analysis: SAFETY Center: ALL CENTERS  
 Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Body System/ Adverse Event	PLACEBO + MTX	MRA 4 MG/KG + MTX	MRA 8 MG/KG + MTX
	N = 392 No. (%)	N = 399 No. (%)	N = 399 No. (%)
PNEUMONIA	2 ( 0.5)	3 ( 0.8)	2 ( 0.5)
GASTROENTERITIS	2 ( 0.5)	2 ( 0.5)	-
CELLULITIS	-	-	2 ( 0.5)
GASTROENTERITIS VIRAL	-	2 ( 0.5)	-
SPINAL COMPRESSION FRACTURE	1 ( 0.3)	-	3 ( 0.8)
BASAL CELL CARCINOMA	-	2 ( 0.5)	-
PROSTATE CANCER	-	2 ( 0.5)	-

Percentages are based on N.  
 Multiple occurrences of the same adverse event in one individual counted only once.  
 Events on escape therapy are excluded  
 AE11 17APR2008:20:42:19 (PDRD)