European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

RoActemra

International Nonproprietary Name: tocilizumab

Procedure No. EMEA/H/C/000955

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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List of Abbreviations

ACR	American College of Rheumatology
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
BMI	Body Mass Index
CBR	Cytokine binding region
CDR	Complementarity determining region
CHO	Chinese hamster ovary
CI	Confidence Interval
CIA	Collagen-induced arthritis
CL	Clearance
Cmax	Maximum Concentration
CMH	Cochran-Mantel Haenszel
Cmin	Concentration at the End of the Dosing Interval (Trough Concentration)
CRP	C-reactive protein
Ctrough	trough concentrations
CV	Coefficient of variation
CYP	Cytochrome
DAS	Disease Activity Score
DMARD	Disease modifying anti-rheumatic drug
DTH	delayed-type hypersensitivity reaction
EIA	Enzyme immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FcRN	Neonatal Fc receptor
GCP	Good Clinical Practice
GD	Gestation day
GI	Gastrointestinal
gp130	Glycoprotein 130 (signaling complex)
h	Hour
HAHA	Human Anti-Human Antibodies
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCP	host cell protein
HDL	High density lipoprotein
IEC	ion exchange chromatography
IgG	Immunoglobulin G
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2

IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
IPC	In-process control
ITT	Intent-to-Treat
IV	Intravenous
KD	Equilibrium dissociation constant
MCB	master cell bank
mIL-6R	Membrane bound interleukin-6 receptor
MR16-1	Mouse specific interleukin-6 receptor antibody
MRA	Myeloma receptor antibody
MTX	Methotrexate
NOAEL	Non observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetic(s)
PP	Per Protocol
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SD	Standard deviation
SF-36	Short form health survey
sIL-6R	Soluble interleukin-6 receptor
SJC	Swollen joint count
sJIA	Systemic Juvenile Idiopathic Arthritis
T½ (α)	Initial half-life
T½ (β)	Terminal half-life
TB	Tuberculosis
TCZ	Tocilizumab
TFF	tangential flow filtration
TJC	Tender joint count
TNF	Tumor necrosis factor
ULN	Upper Limit of Normal
VAS	Visual analogue scale
Vss	Volume of Distribution at Steady-State

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Roche Registration Ltd. submitted on 29 November 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for RoActemra, through the centralised procedure falling within the Article 3(1) and point 1.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended

The applicant applied for the following indication:
Treatment of moderate to severe active rheumatoid arthritis in adult patients who:

- have not been previously treated with traditional disease modifying anti-rheumatic drugs (DMARDs) or
- have an inadequate response to one or more traditional DMARDs or
- have an inadequate response or are intolerant to a tumour necrosis factor antagonist.

Tocilizumab Roche can be given as monotherapy or in combination with methotrexate (MTX) and / or other traditional DMARDs.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 24 May 2007 and 20 September 2007. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status:
At the time of submission of the application, tocilizumab was licensed in Japan for the treatment of Castleman's disease.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Schneider Co-Rapporteur: János Borvendég

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 29 November 2007.
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008.
- During the meeting on 21-24 April 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 April 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 July 2008.
- An inspection of the following site Chugai Pharma Manufacturing Co., Ltd. was carried out between 23 June and 3 July 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 September 2008.
- During the CHMP meeting on 22-25 September 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 20 October 2008.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 4 November 2008.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 16 November 2008.
- During the meeting on 17-20 November 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to RoActemra on 20 November 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 20 November 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Rheumatoid arthritis (RA) is a chronic, potentially debilitating disease that is currently treated by conventional and biotechnologically produced immunosuppressive agents. Although a several potent drugs are available there is still a considerable therapeutic failure rate observed, necessitating new treatment strategies.

The rationale for Development of tocilizumab in RA has been supported by extensive studies demonstrating that IL-6 is a pleiotropic pro-inflammatory multi-functional cytokine produced by a variety of cell types including various types of lymphocyte, fibroblasts, synoviocytes, endothelial cells, neurons, adrenal glands, mast cells, keratinocytes, Langerhans cells, astrocytes and colonic epithelial cells. Elevated levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders including RA. Instrumental in RA pathophysiology, IL-6 has been shown to be involved in processes such as T-cell activation, differentiation of B cells into immunoglobulin-secreting plasma cells, maturation of megakaryocytes leading to platelet production and is now well recognized to stimulate the production of acute phase proteins by hepatocytes. IL-6 also induces the synthesis of the iron regulatory peptide hepcidin during inflammation.

Tocilizumab (RO4877533, TCZ), also referred to as myeloma receptor antibody (MRA), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against the soluble and membrane-bound interleukin 6 receptor (IL-6R). *In vivo*, tocilizumab has been shown to prevent onset of bone and cartilage destruction in a collagen-induced arthritis model in cynomolgus monkeys.

The clinical development of tocilizumab for the treatment of RA includes two dose-finding Phase II studies and five well-controlled Phase III studies investigating the use of tocilizumab, administered either as monotherapy or in combination with methotrexate (MTX) and/or other commonly prescribed disease modifying anti-rheumatic drugs (DMARDs), to adults with moderate to severe, active RA. Long-term safety information and data supporting the durability of efficacy are derived from two long-term open-label uncontrolled observation studies into which patients who completed the 24-week pivotal Phase III studies were eligible for enrolment.

The initially proposed therapeutic indication is as follows:

"for the treatment of moderate to severe active rheumatoid arthritis in adult patients who:

- have not been previously treated with traditional disease modifying anti-rheumatic drugs (DMARDs) or
- have an inadequate response to one or more traditional DMARDs or
- have an inadequate response or are intolerant to a tumour necrosis factor antagonist.

Tocilizumab Roche can be given as monotherapy or in combination with methotrexate (MTX) and / or other traditional DMARDs."

After review of the dossier, the indication has been revised and approved by the CHMP as follows:

"RoActemra, in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate."

RoActemra is supplied as a sterile liquid concentrate for solution for intravenous (iv) infusion available at a concentration of 20 mg/mL. Three presentations of tocilizumab are intended for registration. These are 80 mg, 200 mg and 400 mg and have been selected to provide flexible combinations over the likely body weight range of patients

2.2 Quality aspects

Introduction

Tocilizumab, the active ingredient of RoActemra, is a humanised monoclonal antibody directed against the human interleukin-6 receptor (IL-6R) and is produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology.

The fermentation process is a serum-free process. The cell culture filtrate is purified by a series of chromatography steps, ultra-diafiltration steps and viral inactivation and filtration steps.

The drug product manufacture consists of the formulation of the drug substance with excipients, sterile filtration, aseptic filling into vials, stoppering and capping.

RoActemra is presented as a concentrate for solution for infusion (20 mg/ml) in single-use vials.

Active Substance

Nomenclature

INN Name:	tocilizumab
Compendial Name:	not applicable
USAN/JAN:	tocilizumab
Laboratory Code Name:	RO4877533
CAS Registry Number:	375823-41-9
Other Names:	- recombinant humanised anti-human IL-6R monoclonal antibody - MRA

Description of the active substance

Tocilizumab is a recombinant humanised monoclonal antibody of IgG1κ subclass composed of two heavy chains and two lights chains, with 12 intra-chain and 4 inter-chain disulfide bonds.
The N-linked glycostructures present in tocilizumab include complex-type oligosaccharide structures (see Section "Characterisation").
The total molecular weight of the glycoprotein is approximately 149 kDa.

- Manufacture

The drug substance manufacturing, release testing and stability testing for commercial batches is performed by Chugai Pharma Manufacturing Co. Ltd, Utsunomiya Plant, 16-3 Kiyohara Kogyodanchi, Utsunomiya-city, Tochigi, 321-3231, Japan.

Development genetics
CHO DXB11 cells, derived from a CHO K1 strain, were transfected with an expression vector containing the genes encoding tocilizumab heavy and light chains as well as the DHFR gene.

Transfected CHO DXB11 cells with the DHFR+ phenotype were selected and then cultured in stepwise-increasing concentrations of MTX. Cells were selected for resistance to MTX. By this process, an integrated copy of the DHFR sequence and the flanking regions (i.e. the tocilizumab-encoding sequence) were co-amplified. From the cells obtained, CHO V4 cells were cloned for use as seed cells for tocilizumab production.

Cell bank system

A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) has been developed and maintained in accordance to cGMP and ICH guidelines.

The CHO V4 seed cells were adapted to growth in suspension culture in a serum-free medium, leading to the establishment of the original MCB (MCB-M1) and the original WCB (WCB-M1).

MCB-M1 was modified during development to generate a new MCB (MCB-M2971) and WCB (WCB-M2971). Finally, the current WCB (WCB-M2033) was established from MCB-M2971 by replacement of animal-derived raw materials, with the exception of some bovine milk and salmon-derived additives.

Procedures followed for the preparation of MCB and WCB have been appropriately described. An extensive range of tests has been performed for their characterisation, in accordance with ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Fermentation process

A vial of WCB-M2033 is thawed and cells are expanded in a series of spinner flasks in a selective serum-free growth medium to generate the cell inoculum. A series of bioreactors with increasing volumes is then used to expand the cell mass to generate sufficient cells for the inoculation of a production bioreactor.

Following the production phase, the bioreactor content is harvested using tangential flow filtration (TFF) in order to remove cells from the cell culture medium. The resulting cell culture filtrate is then further purified (see below).

Cell culture conditions and in-process controls (IPC) have been sufficiently described and are considered appropriate.

Purification process

The purification process starting from the cell culture filtrate comprises the following steps, successively:
- Protein A chromatography;
- Viral inactivation step;
- Anion exchange chromatography;
- Mixed-mode ion exchange chromatography;
- Ultra-diafiltration (UF-DF);

- Nanofiltration;
- Final filling and storage

Each step of the purification process has been adequately described, including description of the different buffers used, column regeneration and storage conditions of both columns and product after each step. Suitable IPC controls are in place, with acceptable limits.
Reprocessing is not performed in the manufacturing process of the drug substance.

Manufacturing process development and process validation

The manufacturing process for tocilizumab drug substance has evolved over time in four main stages: "1st generation" (G1) process to "4th generation" (G4) process corresponding to the commercial process. During process development, the cell culture media used for tocilizumab fermentation process changed several times to reduce the use of components derived from animal sources.

The G4 process was developed to increase product yield. This included manufacturing site transfer with scale up in fermentation and purification, optimisation of the cell culture media and fermentation parameters.
Materials obtained from the G4 process were used in phase III clinical studies.

Manufacturing process development data were considered satisfactory. For filiation assessment, extensive structural, physicochemical and biological analyses of materials manufactured pre- and post-change were conducted prior to the implementation of each new manufacturing generation.

The tocilizumab manufacturing process was validated using data from commercial scale and scale-down models with respect to consistency and robustness of process performance and quality attributes, according to approved validation protocols. It was demonstrated that the G4 process consistently maintains process parameters within specified ranges and meets acceptance criteria for performance indicators. Overall, process validation was considered satisfactory.

Characterisation

A) Elucidation of structure and other characteristics:
A comprehensive set of analytical methods was applied to characterise the structure of tocilizumab drug substance derived from the G4 process. Characterisation was performed with respect to the covalent as well as the higher order structure of the tocilizumab molecule and also included the assessment of the heterogeneity with respect to glycosylation and charge-based isoforms.

A1) Physicochemical characterisation:

The complete amino acid sequence of tocilizumab was confirmed and the primary, secondary and tertiary structure were analysed.

It was confirmed that the disulfide linkages in tocilizumab drug substance reflect the disulfide structure known for IgG1 molecules.

Monosaccharide composition was analysed and the types and amounts of monosaccharides identified (N-acetylglucosamine, fucose, mannose and galactose) reflect what is expected for IgG1 molecules.

Analysis of the oligosaccharide composition has shown that the major glycostructures are constituted by core-fucosylated biantennary complex-type oligosaccharide structures differing in the degree of terminal galactosylation, i.e. containing two (G(2)), one (G(1)-1, G(1)-2) or no (G(0)) galactose residues. Besides the major glycostructures, afucosylated (G(0)-F, G(1)-1-F, G(1)-2-F, G(2)-F) and high mannose type

oligosaccharides (M5) are present in tocilizumab. Sialylated oligosaccharides and other high mannose type structures (for example M6, M7) are present at even lower levels.

Ion exchange chromatography (IEC) revealed the presence of several isoforms. Structural characterisation of these isoforms demonstrated that differences between the isoforms are largely due to C- and N-terminal heterogeneity of the heavy chain and incomplete cleavage of the signal sequence from the N-terminus of the light chain.
Investigation of charged-based isoforms was performed.

The structural integrity of the tocilizumab molecule was tested.

Size exclusion chromatography (SEC) was performed to analyse the size distribution of tocilizumab molecule. The two peaks detected in the chromatograms correspond to the monomer and dimer of tocilizumab molecule.

A2) Biological characterisation:

In the cell-based bioassay, the cell growth-inhibiting activity by tocilizumab was evaluated by addition of tocilizumab and IL-6 to the cells such that they compete for the IL-6R on the cell.

The binding activities of tocilizumab to human soluble IL-6R were also assessed.

In vitro data confirmed that tocilizumab has essentially no or minimal complement dependent cytotoxicity (CDC) activity and no significant antibody-dependent cellular cytotoxicity (ADCC) activity.

B) Impurities:

Product-related substances correspond to isoform peaks observed by IEC as well as the dimer and the degradation peaks observed by SEC of tocilizumab drug substance.

Potential process-related impurities include:
- Cell substrate derived impurities: host cell proteins (HCP) and DNA;
- Cell culture derived impurities;
- Downstream-derived impurities such as leached Protein A;
- Other impurities including endotoxin, bioburden;

- Specifications

The drug substance release specifications have been suitably justified and are supported by consistent data from multiple lots. The specifications contain tests for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, quantity, potency.

- Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance with current ICH guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.

The stability data provided were within the specifications and support a shelf life of 24 months at ≤ -50°C for the drug substance.

Medicinal Product

- Pharmaceutical development

RoActemra is presented as a concentrate for solution for infusion in a single-use Type I glass vial. The concentrate is to be diluted in 0.9% sodium chloride prior to administration.

Each vial contains 80 mg, 200 mg or 400 mg of tocilizumab formulated with sucrose, polysorbate 80, disodium phosphate dodecahydrate and sodium dihydrogen phosphate dihydrate and water for injections. These excipients are commonly used in formulating protein pharmaceuticals. Buffer, polysorbate 80 and sucrose are optimised to prevent protein aggregation that may occur in the vial on storage.

The main changes to the formulation occurred during early clinical development and consisted of the removal of D-mannitol followed by the change of sodium chloride for sucrose.

- Adventitious agents

Tocilizumab is produced in a serum-free culture medium without use of human- or animal-derived components; only fish, milk-derived and salmon-derived raw materials are added during the fermentation of tocilizumab. This minimises a possible contamination with adventitious agents.

Compliance with the Note for Guidance on "*Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*" (EMEA/410/01 rev 02) has been sufficiently demonstrated.

Extensive screening for viruses was performed. The tests did not reveal the presence of any viral contaminant in the cells used for production of tocilizumab, with the exception of intracellular A-type and C-type retroviral particles. Such particles are well known to be present in CHO cells. This is acceptable since there is sufficient capacity within the tocilizumab manufacturing process for reduction of this type of viral particles.
The purification process of tocilizumab includes several steps for inactivation/removal of enveloped viruses. Viral safety has been sufficiently demonstrated.

- Manufacture of the product

The drug product is manufactured at Chugai Pharma Manufacturing Co. Ltd, Utsunomiya Plant, 16-3 Kiyohara Kogyodanchi, Utsunomiya-city, Tochigi, 321-3231, Japan.
The secondary packaging of the drug product is carried out at F. Hoffmann-La Roche Ltd, Wurmisweg, CH-4070 Kaiseraugs, Switzerland.
Quality control testing and EU batch release of the drug product is performed at Roche Pharma AG, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany.

Frozen tocilizumab drug substance is thawed and then stored until use (validated maximum storage period of 7 days).
The drug product manufacturing process consists of formulation steps followed by an initial filtration of the formulated bulk solution (optional re-processing step), sterile filtration of the formulated bulk solution, aseptic filling into vials, stoppering and capping steps.
There are no intermediates isolated during the manufacture of the drug product.

The media fill and process validation results, lot-to-lot consistency data and critical process controls have shown that the sterile filtration and aseptic filling steps are robust and well controlled and that the drug product can be consistently manufactured.

- Specifications

Appropriate specifications have been developed. The specifications contain tests for pharmacopoeial methods as well as specific methods.

- Stability of the drug product

Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of drug product. On the basis of the data provided, the approvable shelf life for the drug product is 30 months at 2-8°C.

Discussion on chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

From a Quality point of view, no Major Objection was raised during the evaluation procedure. However, the applicant was asked to clarify several aspects. These points have been solved.

The generation of the original cell line, from the expression construct to the selection process was well described. Cell banks have been established and adequately characterised.

The drug substance manufacturing process is well described. In-process controls (IPC) have been defined and the proposed action limits are acceptable.

Process validation data is satisfactory. In the scale-down models for the chromatography steps, the column diameters were linearly reduced while the bed heights and linear flow rates were maintained. The applicant confirmed the suitability of these models for viral clearance validation.

Manufacturing process development data is satisfactory. For filiation assessment, extensive structural, physicochemical and biological analyses of materials manufactured pre- and post-change were conducted prior to the implementation of each new manufacturing process generation (G1, G2, G3 and G4, successively).

The drug substance has been well characterised. Sources of heterogeneity have been assessed in detail using a wide variety of state-of-the-art techniques. The test methods chosen are considered adequate.

Overall, impurities have been adequately identified and characterised.

The pharmaceutical development of the drug product was considered satisfactory.

The drug product manufacturing process, together with IPCs, have been adequately described; critical steps have been defined and the proposed limits are acceptable. Process validation was considered acceptable.

The description and validation of analytical procedures for the drug substance and drug product were generally satisfactory except for certain methods for which additional information was requested. These issues have been solved.

The applicant has revised the specifications; the acceptance criteria for several tests have been tightened as requested and the available data re-analysed accordingly. In addition, the suitability of the current tests to detect the major variants has been demonstrated.

On the basis of the stability data provided, the proposed shelf life of 24 months at ≤-50°C for the drug substance and 30 months at 2-8°C for the drug product are considered acceptable.

Viral safety and safety concerning other adventitious agents including TSE are sufficiently assured.

Chugai Pharma Manufacturing Co. Ltd, which is the manufacturing site for the drug substance and drug product, was inspected by the German inspectorate in July-August 2008. Several major deficiencies were identified. The applicant provided a corrective action plan that is acceptable. It can now be considered that this site is operated in accordance to current EU Good Manufacturing Practices (GMP).

2.3 Non-clinical aspects

Introduction

Non-clinical toxicity studies were conducted in compliance with the good laboratory practice (GLP) regulations. Safety pharmacology studies, including cardiovascular safety studies in the cynomolgus monkey, conducted during preclinical development were not done under formal GLP requirements. In addition, a further series of non-GLP investigations was also conducted as part of regulatory GLP-studies in order to address specific safety aspects of tocilizumab.

Pharmacology

- Primary pharmacodynamics

Tocilizumab is a recombinant humanized anti-human interleukin-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin IgG1 subclass. IL-6 is a multi-functional cytokine, produced by a variety of cell types and involved in T-cell activation, induction of acute phase proteins and stimulation of haematopoiesis.

IL-6 has been implicated in the pathogenesis of various diseases, including inflammatory diseases, RA, inflammatory bowel disease, osteoporosis and neoplasia. IL-6 exerts its biological activities through its receptors, membrane-bound IL-6 receptor (mIL-6R) and soluble IL-6 receptor (sIL-6R). Due to restricted expression of the cognate mIL-6R, signalling via the membrane-bound pathway is confined to only a small population of cell types, which includes neutrophils, monocytes, T-lymphocytes, B-lymphocytes, hepatocytes, osteoblasts and keratinocytes. However, the number of cell types expressing mIL-6R does not reflect the full spectrum of cell types that can respond to IL-6. IL-6 can activate cells that do not express the IL-6R through a process known as trans-signalling. In this process, IL-6 first binds to free sIL-6R, then the IL-6/sIL-6R complex binds to the common signal-transducing molecule [glycoprotein 130 (signalling complex) gp130, which is expressed on the surface of most cells. This process enables cells that do not possess the cognate mIL-6R to respond to IL-6 signalling.

The preclinical pharmacology programme showed that tocilizumab specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R with similar affinity. Therefore, tocilizumab is able to block IL-6 from binding to both receptors and thereby blocks the activity of IL-6. *In vitro* studies demonstrated that tocilizumab can inhibit IL-6 binding to and displace already bound IL-6 from sIL-6R and that tocilizumab has a strong anti- IL-6 effect. Tocilizumab is specific to the IL-6R with no binding to other receptors associated with gp130 or to receptors for other cytokines. Preclinical studies showed specificity of tocilizumab to the IL-6R with no direct cross-reactive inhibitory effect on TNF-α, IL-1β, IL-15 or IL-2 *in vitro*.
The cynomolgus monkey was chosen as the pharmacologically relevant species because tocilizumab cross-reacts with monkey IL-6R under *in vitro* and *in vivo* conditions. In a cynomolgus monkey model of collagen-induced arthritis (CIA), tocilizumab was shown to prevent both the local joint and the systemic inflammatory disease manifestations.

- Secondary pharmacodynamics

Tocilizumab does not bind to IL-6R of rats, mice and rabbits. Tests in non-responder species are of very limited value for target-specific molecules, such as therapeutic antibodies. Studies did not show any evidence for off-target effects of tocilizumab.

- Safety pharmacology programme

The *in vivo* immunomodulatory consequences of inhibition of IL-6R signalling were investigated in studies in mice using the mouse specific IL-6R antibody MR16-1. The studies demonstrated that IL-6 inhibition per se does not affect the primary antibody response to a T-cell dependent antigen. The delayed-type hypersensitivity reaction (DTH) was only reduced when IL-6R signalling was blocked during the induction phase but had no effect at later phases. The data suggests an overall effect of inhibition of IL-6R signalling on T-cell priming rather than on T-cell differentiation, IL-6R inhibition did not affect the development of T-cell memory and T-helper cell activity.
The cardiovascular safety of tocilizumab has been investigated in a series of preclinical *in vivo* studies in cynomolgus monkeys. Tocilizumab showed no effect on the cardiac electrophysiological performance, cardiac tissue integrity or systemic pro-thrombotic activities IV at doses up to 50 mg/kg.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not conducted with tocilizumab.

Pharmacokinetics

In a single dose intravenous study in rats values of ca. 200 h for terminal half-life, ca. 0.6 ml/h/kg for total CL and ca. 160 ml/kg for the distribution volume (Vss) were calculated after doses of 0.5, 5 and 50 mg/kg, respectively. Dose proportional increase in AUC was observed.

From single dose intravenous studies in male cynomolgus monkeys values of 0.5 and 0.2 ml/h/kg for total CL and of ca. 60 ml/kg for the distribution volume (Vss) were calculated after the 5 and 50 mg/kg dose, respectively. A clear biphasic decline was observed. The comparability of the results for the 5 mg/kg dose obtained in a study with female monkeys suggests that there are no pharmacokinetic differences due to gender in monkeys. An apparent non-linear pharmacokinetic behaviour in the monkeys was observed (dose dependent values for CL and over-proportional increase in AUC) which was more pronounced between the lower doses (0.5 and 5 mg/kg) than between the 5 and 50 mg/dose groups. This resembles the findings in humans.

The small values for the volume of distribution found in both species of about 1.5 to 2 times the plasma volume indicate a low tissue penetration of tocilizumab comparable to other IgG molecules. From one study in monkeys using the s.c. route of administration a bioavailability of 72% was calculated after a dose of 5 mg/kg.

A multiple-dose study in cynomolgus monkeys indicated that pharmacokinetics of tocilizumab did not change upon repeated administration over 8 weeks. Neutralizing anti-tocilizumab antibodies could be detected in plasma of cynomolgus monkeys after single and repeated dosing which were possibly responsible for an apparently accelerated decline in plasma concentration of tocilizumab at later time points in the single dose study.

A distribution study in cynomolgus monkeys revealed tissue/plasma ratios of tocilizumab > 1 for some tissues at day 28 p.i.. In most cases the ratios increased from day 7 to day 28 suggesting slow equilibration between plasma and tissues. A 10fold higher concentration in the synovial fluid than in plasma was observed at day 28. Binding to blood cells was rather low, ca. 20% of total tocilizumab in blood

circulation seems to be bound to/in blood cells. The extent of binding to plasma proteins, especially to the soluble receptor sIL-6R, has not been determined in animal plasma.

Consistent with its nature as IgG, tocilizumab seems to be able to cross the placental barrier. In a segment II-embryo-foetal development study in cynomolgus monkeys foetal plasma concentrations of tocilizumab were 39% and 60% of the maternal plasma concentration after application of 10 and 50 mg/kg/day, resp.

There is agreement that catabolism pathways similar to the known pathways for IgG molecules can be assumed for tocilizumab. Regarding the Neonatal Fc receptor (FcRn)-mediated pathway a critical value is the affinity of tocilizumab to this receptor. The binding of tocilizumab to the human neonatal Fc-receptor (FcRn) was studied *in vitro* by surface plasmon resonance analysis. Based on the results of this study, it is concluded that tocilizumab shows an affinity to human FcRn similar to that of other therapeutic IgGs (trastuzumab and rituximab). Thus, these data provide evidence that tocilizumab undergoes the same FcRn-mediated clearance and transcytosis processes that have been described for other IgGs. From *in vitro* binding studies at Fc-receptors on PBMC, it is assumed that binding of tocilizumab to the FcγI receptor occurs in the expected nanomolar range for an IgG.

Chromatographic measurements allowing for the detection of metabolites in plasma indicate that tocilizumab is present in plasma mainly as unchanged tocilizumab. An additional peak (5%) was found in monkey plasma which was attributed to a tocilizumab-2xsIL6R-complex. The meaning of this observation is unclear unless circulating levels of s-IL6R and of the possible complex are measured in parallel and are compared in monkeys/humans/different disease states.

Renal excretion of intact tocilizumab (measured by Enzyme Immunoassay (EIA)) was negligible in both rats and monkeys. Radioactivity was primarily recovered from urine as small molecular weight entities (small peptides, amino acids and/or free ^{125}I) in both rats and monkeys, faecal recovery was very low. These results are consistent with the known elimination behaviour of IgG which undergo little if any renal or biliary excretion but mainly catabolism by proteolysis in lysosomes. The resulting small peptides and amino acids subsequently may be excreted or added to the endogenous amino acid pool.

An *in vitro* study on hepatozytes indicates that the down-regulation of cytochrome (CYP) isoenzymes by IL-6 (mainly CYP3A4) is mediated via the IL-6 receptor, since tocilizumab is shown to inhibit this IL-6 effect on hepatozytes *in vitro*. However, the relevance is not clear since this IL-6 down-regulating effect occurred at very high concentrations only. But it cannot be excluded that tocilizumab might indirectly influence the expression level of CYP enzymes in RA patients by inhibiting the down-regulating effect of IL-6. Co-administered drugs metabolised by this pathway could then be metabolised faster in the presence of tocilizumab.
Comparison of the pharmacokinetics of tocilizumab with that of an intentionally altered tocilizumab variant, in which the terminal galactose of the glycosylation had been enzymatically removed (G0-enriched tocilizumab) following single intravenous administration to rats revealed very similar noncompartmental pharmacokinetic parameters indicating that changes in galactosylation did not change tocilizumab pharmacokinetics in rats. Together with results from *in vitro* binding studies with lectins it can be assumed that tocilizumab has no relevant affinity for galactose-recognizing glycoprotein receptors and that such glycoprotein receptors are unlikely to contribute to the *in vivo* clearance of tocilizumab.

Toxicology

The cynomolgus monkey was chosen as the relevant responder species and a comprehensive toxicology program was conducted with single- and multiple-dose studies up to duration of 6 months to characterize the overall safety of tocilizumab. Additionally supportive data from diverse studies conducted with the rodent analogue MR16-1 also were included in the assessment of the data.

The cardiovascular safety of tocilizumab has been investigated in a series of rigorously designed preclinical *in vivo* studies in cynomolgus monkeys. These results indicate that tocilizumab does not adversely affect cardiac integrity or electrophysiology; neither was an alteration of blood pressure observed in any of the preclinical studies.

Toxicity studies have shown tocilizumab to be 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 monkey studies was 8-to10-fold above the maximum human exposure comparing trough levels in the animals with the maximum level measured in clinical trials. Changes in haematological parameters were observed, e.g. decrease in red blood cell count or increased lymphocyte count.

A signal toward reduction of neutrophils was observed in the 2-week toxicity study with a clear pronounced manifestation in the 4-week daily treatment cynomolgus study with no manifestation in the bone marrow. The absence of bone marrow myeloid hyper or hypoplasia in the presence of reduced absolute neutrophil counts (ANCs) along with the lack of neutrophil morphological abnormalities strongly suggests that neither peripheral sequestration nor incomplete granulopoiesis is the underlying mechanism of the reduced circulating neutrophils.

As expected from differences between human and cynomolgus monkey heavy- and light chain immunoglobulin sequences, tocilizumab is immunogenic in the monkey. The observed anti-tocilizumab response showed a clear inverse dose relationship, an effect which is frequently observed with molecules of this type. Neutralizing antibodies were either greatly diminished or not detected in animals treated with high dose tocilizumab. Thus, the observed immunogenicity of tocilizumab in cynomolgus monkey studies did not compromise the results of these studies and their relevance for risk extrapolation to humans.

The studies demonstrated that inhibition of IL-6 normalizes the inflammation-driven osteoclastic bone destruction and safety studies conducted with tocilizumab demonstrated that a morphologically and functionally normal bone homeostasis is maintained under continuous chronic IL-6 inhibition with tocilizumab.

- Reproduction Toxicity

A reproductive teratology study was performed to address potential effects on embryo-foetal development, and supplementary data from IL-6 knock out (k.o.) and IL-6 transgenic mouse models were evaluated for functional and developmental risk assessments. The effect of tocilizumab on embryonic development has been evaluated in an embryofoetal toxicity study in cynomolgus monkeys in doses up to 50 mg/kg/day. The absence of any teratogenic/dysmorphogenic potential of tocilizumab concurs with the normal phenotype reported for IL-6 deficient mice strains. Neither an abnormal phenotype nor any effect on reproductive performance as consequence of IL-6 depletion has been reported. Nonclinical data suggest that IL-6 is not regarded as a growth factor critical for the development of the musculo-skeletal system and growth and development of other organ systems and is obviously also not critical for the immunological control of the maternal/foetal interface.

A higher incidence of abortion/embryo-foetal death was observed in the cynomolgus teratology study in the 50 mg/kg/day high-dose group with systemic exposure of factor >100 above the human targeted efficacious plasma concentration. Therefore the NOAEL for this study is 10 mg/kg/day due to the possibly treatment-related abortion observed as statistically significant at a dose level of 50 mg/kg/day. But already in the 10 mg/kg/day group there were more abortion compared to the control and the 2 mg/kg/day group. The abortions observed in the study are unlikely to be a consequence of direct embryo-toxicity induced by tocilizumab. The transport of immunoglobulin G (IgG) across the transplacental barrier is dependent on the stage of gestation. The IgG transfer is low or absent in the first trimester, increases at around gestation

day (GD) 60 and is most effective in the last trimester of gestation. However, foetal exposure to tocilizumab at the time when the abortions occurred is considered to be nearly absent. This suggests an underlying maternal rather than a direct foetotoxic effect. The findings cannot be explained by the tocilizumab mechanism of action. Interleukin-6 (IL-6) does not play a critical regulatory role in the control of pregnancy. In female IL-6 deficient mice, no abnormality of implantation was observed. This is in contrast to other factors of the IL-6 cytokine family that have a central regulatory function in the early physiological processes of implantation. Both *in-vitro* and *in-vivo* studies consistently demonstrated that IL-6 does not have a recognized role in the physiology of pregnancy. IL-6 deficient mice represent the most sensitive experimental model to assess such functionality. In IL-6 deficient mice, the reproductive performance investigated did not show a clinically relevant difference in female reproductive parameters such as litter size and neonatal loss compared to the wild-type background strains of mice

Nonclinical data do not suggest an effect on fertility under treatment with tocilizumab as effects on endocrine active organs or on organs of the reproductive system were not seen in a chronic primate toxicity study. There is also no preclinical evidence, that IL-6 signalling is involved in processes of reproduction, and, accordingly, the reproductive performance is not affected in IL-6 deficient mice. Neither monkeys exposed to tocilizumab over more than 6 months, nor IL-6 k.o. mice showed morphological alterations to the primary or secondary tissues of their immune system nor in any other organ or tissues, demonstrating that IL-6 does not play a critical role in organ or tissue development at any stage.

- Other toxicity studies

In clinical trials, mild and moderate elevations of hepatic transaminases have been observed with tocilizumab treatment, but without progression to serious hepatic injury. Increased frequency of these elevations was observed when hepatotoxic drugs were used in combination with tocilizumab or added to tocilizumab monotherapy. Tocilizumab did not affect liver enzymes in cynomolgus monkey studies in which IL-6 was elevated due to CIA induced inflammation. IL-6 is, however, known to have antiapoptotic and growth-promoting effects in hepatocytes. *In vitro* studies conducted with tocilizumab on human hepatoma cell lines have however not been able to clarify this clinical finding. Clinical Precautions and safety monitoring in patients and long-term-extension studies are in development to address this issue. Furthermore serious hepatic events are an endpoint to be followed in pharmacovigilance and in registries; such events will be fully queried using a Guided Questionnaire in clinical studies and in response to spontaneous adverse event reports. Guidance will be provided in the product labelling under Section 2 “Posology and Administration” and Section 4.4. “Special warnings and precautions for use, regarding the monitoring of liver enzymes”.

Ecotoxicity/environmental risk assessment

Tocilizumab is a monoclonal antibody, a protein and as such formally exempted from environmental risk assessment according to the EMEA guideline 4447/00 (2006), which assumes no significant environmental risks arising from proteins. Based on standard acute ecotoxicity tests with algae, daphnia and fish and on lack of evidence for bacterial toxicity, the ecotoxic potential of tocilizumab is considered to be low. The excipients are degradable too and show no significant ecotoxic potential.

Discussion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

The embryo-foetal toxicity study conducted in cynomolgus monkeys showed no evidence of a teratogenic potential of tocilizumab. A slight increase of abortion/embryo-foetal death was observed with high systemic exposure in the highest dose group (exposure > 100 above the expected human efficacious concentration). The relevance of this finding for human pregnancy cannot be excluded.

2.4 Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The assay for measurement of tocilizumab in serum (ELISA) measures "free tocilizumab" only, i.e. tocilizumab with one or two free IL-6R binding sites. It is assumed that the measurement of tocilizumab reflects the total amount of free tocilizumab plus an uncertain fraction of tocilizumab which has been bound to sIL-6R. Furthermore, it is assumed that antibody-bound tocilizumab would not be measured in the assay as well. Therefore, when interpreting PK data it has to be kept in mind that the concentrations refer mainly to free drug. However, the majority of tocilizumab present in human is expected to be free, i.e. not complexed to sIL-6R, as its molar concentration largely exceeds that of sIL-6R.

The main PK results were based on the population PK analysis from 4 Phase III studies in 1793 RA patients with supportive data from non-compartmental analyses of clinical pharmacology studies.
Non-compartmental PK analysis from single and multiple dose studies showed similar PK characteristics in RA patients compared to healthy volunteers. The PK of tocilizumab was characterized by non-linear kinetics over the dose range tested. CL was concentration-dependent. There was no deviation from a dose proportional increase for Maximum Concentration (Cmax) and a more than dose-proportional increase in AUCinf and Concentration at the End of the Dosing Interval (Trough Concentration) **(**Cmin). The over-proportional increase in AUCinf with increasing dose seemed more pronounced between the 2 and 10 mg/kg doses than between the higher doses (10, 20 and 28 mg/kg).RA patients showed mean values of 0,26 ml/h/kg for CL, ca. 160 h for t1/2 and ca. 60 ml/kg for Vss after 10 mg/kg. These values were comparable to healthy volunteers in this dose range. The PK parameters of tocilizumab did not change with time.

The observed concentration-dependency of the tocilizumab CL could be best described by a population PK model rather than by non-compartmental analysis. A two-compartment disposition model with parallel first-order (linear CL) and Michaelis-Menten elimination (nonlinear or concentration-dependent CL) kinetics was obtained which could explain convincingly the dose proportionality of Cmax, the over-proportional increase in AUC and Cmin and the apparent increase of half-life with dose observed in single and multiple dose ascending studies:

The total CL of tocilizumab is concentration-dependent and is the sum of linear CL and nonlinear CL. The portion of the nonlinear CL is reflecting a zero-order process which is saturated at very low concentrations (estimated KM: 2.7µg/ml). This is believed to reflect the target-mediated CL via binding to IL-6R. At higher tocilizumab concentrations, total CL is mainly determined by linear CL which was calculated to be 12.5 mL/h.

Non-linear CL plays a major role at low tocilizumab concentrations. The average contribution of nonlinear CL to the total CL was less for 8 mg/kg than for 4 mg/kg tocilizumab every 4 weeks.
Due to the concentration-dependent total CL a calculated terminal half-life must appear in a "concentration-dependent" manner as well. Therefore, it should not be derived using non-compartmental analysis. Nevertheless, the mean apparent t1/2 of tocilizumab following a single dose of 10 mg/kg was

estimated by non-compartmental analysis to be about 8 days. Based on parameter estimates from the population PK model, the effective t1/2 at steady-state ranged from 8 to 14 days for 8 mg/kg dosing every 4 weeks.

At high concentrations, when nonlinear CL becomes negligible, the apparent t1/2 can be calculated using the formula for a two-compartmental model with the linear CL term only. Applying this formula to tocilizumab results in an apparent t1/2 of 21 days. This estimate of apparent t1/2 is comparable to the t1/2 of human IgG antibodies (ie, around 23 days).

A major conclusion is that due to the concentration-dependent PK, the total CL and/or apparent half-life estimated is only valid for a given dose and dosing interval and should not be translated to other dosing regimens.

As with other immunoglobulins, tocilizumab is not excreted via the renal or biliary route. It can be assumed that tocilizumab is predominantly eliminated via catabolism. Therefore, the total plasma CL_t reflects both degradation (in plasma) and distribution to tissues/endothelial cells where also degradation takes place.

After multiple dosing with 8 mg/kg every 4 weeks, the predicted systemic accumulation ratio is small for Cmax and AUC (1.06 and 1.22, respectively), but higher for Cmin (2.35). For the 8 mg/kg dose, steady-state is achieved following the first administration, after 8 weeks and after 20 weeks for Cmax, AUC and Cmin, respectively. The predicted coefficient of variation (CV) for AUC at steady-state for 8 mg/kg tocilizumab every 4 weeks was 44%.

After administration of the 8 mg/kg dose in a 4-week interval, a mean (± SD) Cmin at steady-state (Ctrough) of 9.7 µg/ml is estimated showing a high variability (CV) of about 100%. This mean Cmin value is close to the KM value (2.7 µg/mL) estimated for the nonlinear CL component, with Cmin being about 3.6-fold higher than KM. Thus, the Ctrough values are in a concentration range where small changes in serum tocilizumab concentrations result in a large change in nonlinear CL. Furthermore, the expected Ctrough value is 65 fold higher than the calculated value for KD of tocilizumab for the binding at the IL-6R (KD about 1 nM = 0.15 µg/ml), thus indicating complete receptor occupancy even at the end of each 8 mg/kg dosing interval.

Estimated volume of distribution during steady state (Vss) was small (6.4 L). This corresponds to 1-2 times the plasma volume which is in accordance with values obtained for other monoclonal antibodies.
Protein binding *in-vitro* and *ex-vivo* or binding to blood cells has not been determined in human plasma.

Results with monkey plasma indicate that during steady state ca. 20% of total tocilizumab concentration in plasma might be bound at/in blood cells.

Consistent with its nature as IgG, tocilizumab seems to be able to cross the placental barrier. In a segment II-embryo-foetal development study in cynomolgus monkeys, foetal plasma concentrations of tocilizumab were 39% and 60% of the maternal plasma concentration after application of 10 and 50 mg/kg/day, respectively. Data in humans are not available.

It is unknown whether tocilizumab is excreted in human breast milk. From its IgG nature it has to be expected.

- Special populations

From the evaluation of the influence of different co-variates on the PK of tocilizumab (population PK) it can be concluded that no dose adjustments are necessary for age, gender or race as these did not affect the PK of tocilizumab. Body size had an effect on CL: With a flat dose, an increase in BW would result in a

decrease in the secondary PK parameters AUC and Cmin. With a BW-adjusted dosing regimen the effect of BW on CL is accounted for. However, the BW-adjusted dosing results in higher exposures with higher BWs (>100 kg) and lower exposure in patients with low body weight < 60 kg (predicted AUC increase almost two-fold from lowest to highest body weight). This did not affect efficacy or safety parameters in a clinically relevant manner. Nevertheless, it is recommended not to exceed a dose of 1200 mg as this was the maximum dose in clinical trials. In order to minimise the risk of insufficient therapeutic response in patients with a body weight <60 kg, a recommendation for a dose capping at 480 mg was introduced.

Although no formal renal impairment studies were conducted, both the results from one study with renal impaired RA patients and from the population PK analysis do not indicate an influence of renal impairment on the main PK variables of tocilizumab. Thus, at least mild renal impairment does not change the PK of tocilizumab. For patients with moderate to severe renal impairment (CLCr < 30 ml/min) no data are available.

Due to the lack of specific metabolism in the liver it is not expected that PK of tocilizumab is altered in hepatic impaired patients. Therefore the influence has not been studied.
Other covariates with a statistically significant influence on the primary PK parameters were High density lipoprotein (HDL)-cholesterol, RF, total protein and albumin, however, these covariates did not change the PK of tocilizumab in a clinically relevant manner.

- Pharmacokinetic interaction studies

The influence on the PK of tocilizumab by other drugs has been addressed in studies for methotrexate (MTX) only. It is known that MTX can decrease the CL of antibodies. The PK data from two studies indicate that MTX appears to have no/little influence on the PK of tocilizumab. However, it cannot be excluded that a small interference is causative for the slight but not significant increase in all four Cmin values during the four dose intervals in the 8 mg/kg groups with co-medication of MTX.

The influence of tocilizumab on the PK of other drugs was investigated in one study for the drugs dextromethorphan and omeprazol. A noticeable influence could only be detected for omeprazol.
The bioavailability of omeprazol (10 mg oral dose) was decreased by about 20-30% after intravenous administration of 8 mg/kg tocilizumab. Since omeprazole is a substrate (and inhibitor) of CYP2C19 this can be explained with an inhibition of the down-regulating effect of IL-6 by tocilizumab.
However, the finding that the CL of dextromethorphan (a CYP3A4 and CYP2D6 substrate) was slightly decreased while the CL of its metabolite dextrorphan (CYP3A4 substrate) was increased (total CL unchanged) is not consistent with the suggestion of a general inhibition of tocilizumab on the down-regulating effect of IL-6 which appeared to affect almost all CYP isoforms *in vitro*. However, this IL-6 effect occurred only at very high concentrations *in vitro*. Thus, the relevance is not clear.

For all other clinically relevant RA medications (NSAIDs, steroids etc.), no data about PK interactions are available except the results from the population PK analysis in which none of the co-medication in all clinical trials was identified as a co-variate influencing the PK of tocilizumab. Since it cannot be excluded that tocilizumab can potentially increase the CL of all co-administered drugs which are metabolized by CYP450 enzymes in the liver, also the CL of several NSAIDs and steroids might be affected. The possible interaction is most important for CYP450 substrates with a narrow therapeutic index (eg, warfarin, cyclosporin). This has been addressed accordingly in the SPC.

There is an ongoing study (WP18663) in 24 RA patients to investigate the PK of MTX and the CYP3A4 substrate simvastatin in combination with a single i.v. dose of 10 mg/kg tocilizumab. Since MTX and simvastatin are important co-medications in RA patients the results of this study are not without significance. This issue is addressed in the Risk Management Plan (RMP).

Pharmacodynamics

- Mechanism of action

Tocilizumab specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R receptors with similar affinity in the nanomolar range. Data from binding studies to modified hIL-6R variants suggested that the binding region of tocilizumab was within in the cytokine-binding region (CBR) to which IL-6 binds. Therefore, tocilizumab is able to block IL-6 from binding to both receptors and thereby blocks the activity of IL-6.

Tocilizumab inhibits both the IL-6 classical and trans-signalling pathways by binding to mIL-6R and sIL-6R. The binding of tocilizumab to the receptor prevents receptor binding to IL-6. The tocilizumab/receptor complex cannot be bioactive since it is unable to effect the dimerization of the gp130 molecule. In the absence of this dimerization, the IL-6 signal is completely blocked.

- Primary and Secondary pharmacology

In healthy volunteers, an increase in IL-6 levels was observed following administration of single tocilizumab doses of 1 and 2 mg/kg. Baseline values of IL-6 were all well below 10 pg/ml as it is expected for healthy volunteers. A clear but variable increase was observed for the 1 and 2 mg/kg doses with peak levels of 10-60 pg/ml occurring between 24 and 72 h post-dose.

In RA patients, administration of single tocilizumab doses resulted in a marked increase in IL-6 after 8 mg/kg and 10 mg/kg. In one multiple dose study peak values of up to 1800 pg/ml have been observed after the 8 mg/kg dose during the first days after administration.

During the 4 pivotal Phase III studies the only sampling time points were pre-infusion and 2 weeks after infusion. For both 4 and 8 mg/kg doses, mean IL-6 levels peaked at week 2. Since this was the only assessed time point these are no true peak values, from the former studies peak values are expected earlier during the first days after infusion. Due to the sparse sampling also the postulated tendency for a decrease in peak levels over time cannot be followed.

The observed increase in IL-6 serum concentrations following infusion of tocilizumab is believed to reflect the binding of tocilizumab to the soluble and membrane-bound IL-6 receptors. Following tocilizumab dosing, tocilizumab binds to the IL-6 receptors and blocks the receptor-mediated CL of IL-6, leading to an increase in serum concentration of IL-6. Across the studies, lower mean trough IL-6 levels were observed for the 4 mg/kg dose compared with the 8 mg/kg dose. Overall, IL-6 trough levels tended to decrease over time. This is believed to reflect the declining production of Il-6 as the inflammatory process is controlled.

A marked and dose-dependent increase in sIL-6R was observed in healthy volunteers and RA patients at single doses ≥ 0.5 mg/kg tocilizumab. With increasing doses, both peak levels (up to 7-fold increase of baseline levels) and time to reach these peak levels increased (about 3 to 4 weeks after the 8 mg/kg dose). Following a single dose of 10 mg/kg to RA patients, peak sIL-6R levels were achieved at 4 weeks post-administration with values returning to baseline approximately 8 weeks post-administration. At multiple doses of 8 mg/kg every 4 weeks, high and sustained sIL-6R levels, with up to a 14-fold increase from baseline, were observed with only a slight fluctuation within the dosing interval.

The increase in soluble IL-6 receptor levels with tocilizumab exposure is believed to be a consequence of the binding of tocilizumab to those receptors. It is hypothesized that the accumulation of sIL-6R in serum with increasing tocilizumab exposure reflects the slow CL of the TCZ/sIL-6R complex.

Using a gel filtration method it has been shown in healthy volunteers after a 2 mg/kg dose, that more than 99% of sIL-6R was bound to tocilizumab. Since the sIL-6R assay measures only an unknown amount of these complexes, i.e. it is underestimating the total sIL-6R levels. Since the clinical relevance for the increase in sIL-6R levels is not clear this discrepancy might not be important. The population PK analysis revealed that sIL-6R did not affect the pharmacokinetics of tocilizumab.
A feedback rise of IL-6 and an up-regulation of IL-6 receptors (and hence sIL-6R) due to the receptor blockade by tocilizumab is conceivable. However, the observed new increase after each dose is not fully consistent with the idea of complete receptor occupancy by tocilizumab throughout the whole interval.

During the first-in-man study MRA001JP a decrease in the complement titres and IL-2 was observed. The observed decreased IL-2 reactivity was questionable due to the inappropriateness of the IL-2 reactivity assay method. IL-2 reactivity has not been measured in subsequent clinical trials. Reduction in complement levels is believed to be consecutive to the inhibition by tocilizumab of IL-6 stimulation of hepatocyte acute phase protein synthesis. Further measurements of the time course of mean CH50, C3 and C4 in patients with RA in several studies in Japan showed that mean concentrations decreased to values around the lower limit of normal and were maintained thereafter. The changes in complement were not clinically significant and were not associated with symptoms suggesting extensive immune complex formation.

After a single dose of 5 and 10 mg/kg tocilizumab in RA patients mean C-reactive protein (CRP) levels decreased markedly between week 1 and week 3 to 4, respectively. For the 5 mg/kg dose, mean CRP levels decreased by about 80%, from 1.7 ± 1.2 mg/dL at day 1 to 0.3 ± 0.1 mg/dL at week 1. By week 6, mean CRP levels had returned to baseline.

In multiple dose studies, a dose-dependent decrease in CRP levels was observed in RA patients with tocilizumab doses ≥ 4 mg/kg. For 8 mg/kg every 4 weeks, CRP levels were markedly suppressed as early as week 2 and sustained around the normal range during the entire dose interval (4 weeks) compared to MTX (no effect on CRP). Only slight fluctuations in CRP were observed with this dose. For multiple doses of 4 mg/kg every 4 weeks, fluctuations in CRP levels were greater than with 8 mg/kg. CRP levels at week 2 post-dose were low and similar to levels for 8 mg/kg. However, for the 4 mg/kg dose, CRP transiently increased at trough which is in clear contrast to what was observed for the 8 mg/kg dose. Therefore, a sustained decrease in CRP throughout treatment duration was achieved for 8 mg/kg every 4 weeks dose only, supporting this dosing regimen for the treatment of RA.

Immunogenicity was monitored in all clinical trials with tocilizumab, the sampling time points during the four pivotal Phase III studies were every 2 weeks up to 24 weeks. A total of 18 out of 1793 RA patients (1%) were positive for anti-tocilizumab antibodies (HAHAs) in the confirmation assay. In addition, the immunogenicity of tocilizumab was assessed as part of the population PK analysis, which investigated the effect of anti-tocilizumab HAHAs on the PK of tocilizumab. HAHAs were not identified as a covariate influencing the PK of tocilizumab.

However, neither the screening/confirmation assay nor the inhibition ELISA are capable to measure already built complexes of tocilizumab-HAHA. Thus, the HAHA-assays measure free antibodies only. Since it must be assumed that most of the HAHAs will be bound to tocilizumab (especially in the presence of high tocilizumab concentrations), the measured HAHAs are probably only a small amount of the total HAHAs built. Secondly, due to the small free portion of the antibodies they might not be detected at all in the studies. Thus, the true incidence of patients who built HAHAs and the quantity HAHAs measured in these patients might be underestimated. The issue of further monitoring immunogenicity is addressed in the RMP.

The exposure-efficacy relationship showed an exposure-dependent decrease in DAS28 (clinical endpoint). Exposure safety relationship showed an exposure-dependent decrease in neutrophil count. PK/PD modelling of both relationships revealed EC50 values for tocilizumab of 3.7 µg/ml (for decrease in

DAS28) and 7.4 µg/ml (for neutrophil loss rate), respectively. Since both the dose-response curves are close together it becomes clear that a positive response will necessarily be accompanied by a certain neutrophil loss rate. Comparing these EC50 values with the predicted values of about 10 µg/ml for Ctrough and about 180 µg/ml for Cmax of tocilizumab during a 8 mg/kg dosing interval, a reduction in Cmax (reduction in infusion rate) might be considerable in order to reduce the risk of very high neutrophil loss rate.

Clinical efficacy

Tocilizumab (TCZ, MRA) is intended for the treatment of moderate to severe active RA. The applicant initially applied for a broad indication covering all clinical situations from first line therapy in previously untreated patients to patients that have failed on one or more anti-TNF medications.

In the pivotal trials TCZ has been studied at two doses, the applied dose of 8 mg/kg every 4 weeks corresponds to the higher of the two studied doses. A combination therapy with MTX, as is common in the setting of RA treatment with biologics, is left at the discretion of the physician.

The clinical development involved five pivotal phase III studies and two long-term extension studies. There are four supportive studies, two phase II studies supporting dosing recommendations and two phase III studies that are central to licensing in Japan.

Table 4; Overview of main studies

Study ID	Design	Diagnosis Incl. criteria	Study Posology	Subjs by arm entered/ compl.	Duration	Primary Endpoint
WA17822	Three-armed, randomised, double-blind, placebo-controlled, parallel group, multicentre	Moderate to severe active RA who had an inadequate response to MTX	Placebo + MTX TCZ 4 mg/kg + MTX TCZ 8 mg/kg + MTX	204 214 205	24 weeks	ACR 20 response rate
WA 17823	Three-armed, randomised, double-blind, placebo-controlled, parallel group, multicentre	Moderate to severe active RA who had an inadequate response to MTX	Placebo + MTX TCZ 4 mg/kg + MTX TCZ 8 mg/kg + MTX	394 401 401	2 years (ongoing)	ACR 20 response rate at week 24 Change from baseline in modified Sharp score and change in physical function at 1 and 2 years
WA18063	Two-armed, double blind, randomised, placebo-controlled	Moderate to severe active RA who had an inadequate response to DMARDs	Placebo + DMARD TCZ 8 mg/kg + DMARD	415 805	24 weeks	ACR 20 response rate

WA17824	Two armed, double blind, double dummy, randomised, placebo-controlled	Active RA; MTX naïve or MTX discontinued, but not due to lack of efficacy or AE	MTX 7.5-20 mg/week TCZ 8 mg/kg q4weeks	284 288	24 weeks	ACR 20 response rate at week 24
WA18062	Three-armed, double blind, randomised, placebo-controlled	Moderate to severe active RA who had an inadequate response to anti-TNF agent(s)	Placebo + MTX TCZ 4 mg/kg + MTX TCZ 8 mg/kg + MTX	160 164 174	24 weeks	ACR 20 response rate at week 24
WA18695	Open label extension study, single arm	Patients completing 17822	TCZ 8 mg/kg q4weeks + MTX	537		Long term safety/efficacy
WA18696	Open label extension study, single arm	Patients completing WA17824, WA18062, WA18063, WP18663	TCZ 8 mg/kg q4weeks alone or plus MTX/DMARD	1902		Long term safety/efficacy

The applicant has designed a comprehensive clinical program that took several relevant patient populations into account, i.e. MTX/DMARD failure patients, anti-TNF failure patients and MTX naïve patients. Comparator for MTX/DMARD failure (study WA17822, WA17823, WA18063) and anti-TNF failure populations (study WA18062) was placebo on the background of stable doses of standard therapy. Study WA17824 compared tocilizumab to MTX in a non-inferiority study.

Endpoints in the clinical trials were very similar in all trials and involved response evaluation according to ACR, DAS28 and patient reported outcomes and were fully compliant with the current "Points to Consider on the Clinical Investigation of Medicinal Products other than NSAIDs in Rheumatoid Arthritis".

- Dose response studies

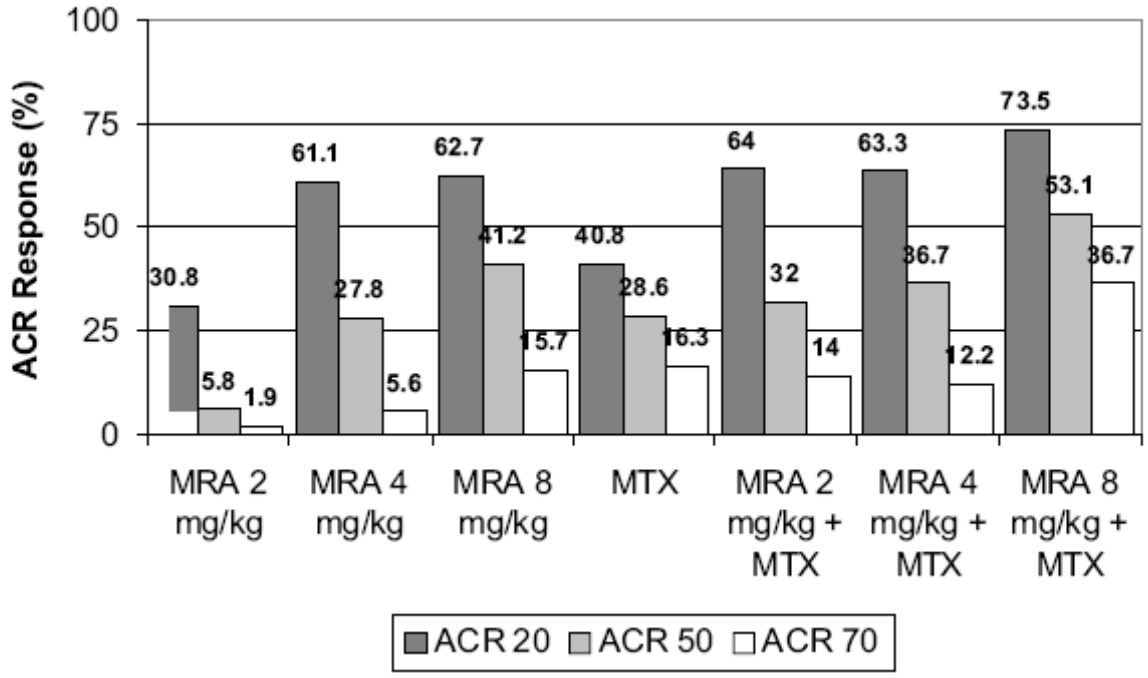
LRO301 was a 20-week Phase II, double-blind, parallel-group, placebo-controlled, randomized, seven-arm, dose-finding study conducted in Europe, with TCZ given alone or in combination with MTX. This was the primary study used to support the doses investigated in the pivotal trials.

The trial consisted of a 4-week run-in phase with weekly MTX (≥10 mg) and folic acid, after which patients entered a 20-week active treatment phase (of four study infusions) and were allocated to one of seven treatment groups: TCZ 2 mg/kg plus MTX placebo, TCZ 4 mg/kg plus MTX placebo, TCZ 8 mg/kg plus MTX placebo, TCZ 2 mg/kg plus MTX, TCZ 4 mg/kg plus MTX, TCZ 8 mg/kg plus MTX or placebo infusion plus MTX. Patients took 5 mg folic acid weekly for the duration of the study. Patients were assigned to one of the seven treatment groups using the minimisation technique stratifying for centre and MTX dose level.

Tocilizumab at a dose of 2 mg/kg in the monotherapy setting was clearly not superior to MTX monotherapy and proved inferior in some aspects. Treatment with doses higher than 2 mg/kg was superior to MTX monotherapy. The 8 mg/kg dose appeared to be the most effective dose across monotherapy as well as combination therapy with MTX. However, there was no clear evidence showing improved efficacy with combination therapy.

The following figure depicts ACR response rate at week 16 (LOCF, FAS population).

Figure 4



In the monotherapy setting, a linear dose-response relationship could be observed, this was less pronounced in combination therapy with MTX. Doses higher than 8 mg/kg were not tested, this is considered acceptable given the dose-response relationship that was observed.

MRA009JP was a randomized, double-blind, placebo-controlled, parallel-group study that evaluated two different dose regimens of TCZ in patients who were not receiving concomitant DMARD. A total of 163 patients from 29 sites in Japan received at least one dose of study medication. The primary endpoint was the proportion of ACR20 responders at week 12 (or the last observation prior to week 12). There was a significantly higher proportion of ACR20 responders in the TCZ groups compared with the placebo group ($p < 0.0001$). Additionally, ACR50 and ACR70 response rates were higher in the TCZ groups than the placebo group (see Table 5 below).

Table 5

	Placebo N=53	TCZ 4 mg/kg N=54	TCZ 8 mg/kg N=55
ACR20	11.3%	57.4%	78.2%
p-value*	-	<0.0001	<0.0001
ACR50	1.9%	25.9%	40.0%
ACR70	0%	20.4%	16.4%

* Treatment comparison with placebo for ACR20 response

- Main studies

WA17822: A randomized, double-blind, parallel group study of the safety and reduction of signs and symptoms during treatment with TCZ vs placebo, in combination with methotrexate (MTX), in patients with moderate to severe active rheumatoid arthritis (RA).

WA17823: A randomized, double-blind, parallel group study of the safety and prevention of structural joint damage during treatment with TCZ versus placebo, in combination with methotrexate (MTX), in patients with moderate to severe active rheumatoid arthritis (RA).

WA17824: A randomized, double-blind, double-dummy, parallel group study of the safety and efficacy of TCZ monotherapy, versus methotrexate (MTX) monotherapy, in patients with active rheumatoid arthritis.

WA18062: A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with TCZ versus placebo, in combination with methotrexate (MTX) in patients with moderate to severe active rheumatoid arthritis (RA) and an inadequate response to previous anti-tumour necrosis factor (TNF) therapy.

WA18063: A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with TCZ versus placebo, in combination with traditional disease modifying antirheumatic drug (DMARD) therapy in patients with moderate to severe active rheumatoid arthritis (RA) and an inadequate response to current DMARD therapy.

WA 18695/18696: Long-term extension study of safety during treatment with TCZ (TCZ) in patients completing treatment in TCZ core studies

METHODS

Study Participants

A total of 4211 adult RA patients from 725 centres worldwide were enrolled in the pivotal Phase III trials. The key patient selection criteria for the pivotal Phase III studies are shown in Table 6 below:

Table 6

	WA17822	WA17823	WA18063	WA17824	WA18062
Inclusion Criteria					
RA duration (ACR criteria) ≥ 6 months ≥ 3 months	X	X	X	 X	X
Joint counts SJC ≥ 6 (of 66) and TJC ≥ 8 (of 68)	X	X	X	X	X
Acute Phase Reactants CRP ≥ 1 mg/dL (10 mg/L) or ESR ≥ 28 mm/h	X	X	X	X	X
MTX • Taking MTX for at least 12 weeks immediately prior to baseline, of which the last 8 weeks must have been at a stable dose of between 10 and 25 mg/week (po or parenteral). • MTX naïve or not treated with MTX within 6 months prior to randomization; did not discontinue MTX as a result of clinically important toxic effects or lack of response	X	X		 X	X
Other DMARDs • DMARDs including biologics other than MTX withdrawn prior to baseline • All previous DMARDs withdrawn • Stable dose of permitted DMARDs (traditional, no biologics) for at least 8 weeks prior to baseline	X	X	 X	 X	X

	WA17822	WA17823	WA18063	WA17824	WA18062
Inclusion Criteria continued					
Previous anti-TNF agents • See under Excluded Previous and Concomitant Medications below • Within one year prior to randomization, experienced an inadequate response to previous or current treatment with etanercept, infliximab or adalimumab because of toxicity or inadequate efficacy*.	X	X	X	X	X
Previous NSAIDs /oral corticosteroids Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if the dose had been stable for at least 6 weeks prior to baseline	X	X	X	X	X
Exclusion Criteria					
Functional class IV as defined by the ACR Classification of Functional Status in RA.	X	X	X	X	X
Excluded Previous or Concomitant Therapy • Unsuccessful treatment with an anti-TNF agent (ie, significant safety issues or lack of efficacy) • Intra-articular or parenteral corticosteroids within four weeks prior to screening.	X X	X X	X X	X X	X

Note: In addition, for study WA17823, patients had to have radiographic evidence of at least one joint with definite erosion attributable to RA, as determined by a central reading site.
* Etanercept ≥ 3 months at 25 mg twice a week (or 50 mg weekly), or at least 4 infusions of infliximab at ≥ 3 mg/kg or adalimumab at a minimum of 40 mg every other week for ≥ 3 months

For all studies, the treatment groups within each protocol were well balanced with respect to demographic and baseline RA characteristics. The study populations were representative of the heterogeneity of characteristics among RA patients with moderate to severe, active disease in terms of the range of disease duration and prior treatments as well as comorbidities and concomitant treatments such as corticosteroids and NSAIDs.

Treatments

In studies WA17822, WA17823, WA18062 and WA18063, patients received TCZ or placebo infusion in combination with MTX or other background DMARD therapy. WA17824 was a monotherapy study.

Table 7

Study Drug	Route	Background therapy	Route
Studies WA17822, WA17823 and WA18062			
TCZ 4 mg/kg every 4 weeks	IV	MTX 10-25 mg/week	Oral or parenteral
TCZ 8 mg/kg every 4 weeks	IV	MTX 10-25 mg/week	Oral or parenteral
Placebo every 4 weeks	IV	MTX 10-25 mg/week	Oral or parenteral
Study WA18063			
TCZ 8 mg/kg every 4 weeks	IV	Stable DMARD alone or in combination	Oral or parenteral
Placebo every 4 weeks	IV	Stable DMARD alone or in combination	Oral or parenteral

WA17824			
Study Drug	**Route**	**Placebo**	**Route**
TCZ 8 mg/kg every 4 weeks	IV	Weekly	Oral
MTX 7.5-20 mg / week (escalating dose)*	Oral	Every 4 weeks	IV
Placebo TCZ every 4 weeks for 8 weeks; then active TCZ 8 mg/kg every 4 weeks**	IV	Placebo MTX weekly	Oral

* All patients were started at 7.5 mg week. If the patient had an inadequate response (any swollen or tender joints) the MTX dose was increased to 15 mg/week at week 4 and to 20 mg/week at week 8.
** In the WA17824 substudy only.

In study WA17824, patients were randomly assigned (in a 1:1 ratio) to either TCZ 8 mg/kg or MTX. In the WA17824 substudy, patients were randomly assigned (in 1:1:1 ratio) to either TCZ 8 mg/kg or MTX (as in the main study), or to receive placebo MTX weekly plus iv placebo every 4 weeks for 8 weeks (2 infusions), followed by TCZ 8 mg/kg as an iv infusion every 4 weeks for the remaining 4 months of the study. Patients continued to receive placebo MTX capsules to maintain the blind (TCZ: placebo). In this study, one 5 mg (2.5 mg capsules) reduction in medication (MTX or its placebo) was permitted for patients who, in the opinion of the treating physician, experienced dose-limiting MTX-related side effects.

The dose could not be increased at any time after the dose had been reduced nor could it be reduced to less than 4 capsules / week.

Adjustments to study medication made for insufficient therapeutic response were permitted in all studies (escape therapy).

Objectives

The primary objective of study WA18063 was to assess the efficacy of TCZ vs. placebo in patients with moderate to severe active RA, with regard to reduction in signs and symptoms over 6 months of treatment in combination with background DMARD therapy. This study was conducted in patients with an inadequate clinical response to current DMARD therapy.

The primary objective of study WA17824 was to assess the efficacy of TCZ monotherapy vs. MTX in patients who had not been treated with MTX within 6 months prior to randomization and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response (as determined by the investigator). This study included a 3-arm randomized, double-blind, double-dummy, parallel-group substudy with a placebo arm (8 weeks of placebo treatment followed by 16 weeks of TCZ 8 mg/kg) as an internal control for efficacy.

With the exception of WA17823, all studies had a 24-week treatment period and the primary endpoint was the proportion of ACR20 responders at week 24. Study WA17823 is an ongoing study with two planned interim analyses, primary endpoints are evaluated at 6, 12 and 24 months. The 6-month primary endpoint was the proportion of ACR20 responders at week 24. The 12 and 24 month primary endpoints are the change from baseline in modified Sharp total radiographic score and change in physical function as measured by the area under the curve for the change from baseline in the Health Assessment Questionnaire - Disability Index (HAQ-DI). After year 2, patients can enter an optional open-label extended treatment period of up to 3 years.

WA18695 and WA18696 are Phase III, open-label, international, multicentre studies, the primary objective of which is to assess the long-term safety of TCZ 8 mg/kg as monotherapy or in combination with background DMARD therapy(ies) with regard to adverse events and laboratory result abnormalities. Secondary objectives include assessment of continuing clinical benefit using the same measures as in the core studies.

Outcomes/endpoints

The primary endpoint in all pivotal studies was based on response criteria defined by the ACR at week 24. The ACR20 response rate (the proportion of patients with an ACR20 response) at week 24 was the primary efficacy parameter in the pivotal Phase III studies. An ACR20 response is defined as at least 20% improvement compared with baseline in both tender joint count (TJC) and swollen joint count (SJC), as well as in 3 out of 5 of the additional parameters shown in Table 7 below.

Secondary efficacy endpoints were based on additional ACR response criteria and the European League Against Rheumatism (EULAR) measures of disease activity, which include defined changes to a disease activity score (DAS) and patient-reported outcomes. ACR and DAS28 are both based on a core set of outcome measures combined to quantify disease activity (continuous variables), together with definitions of improvement (response variables). The core set of parameters is shown below:

Table 8

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

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

In addition to the patient-reported outcomes included in the ACR and EULAR criteria (eg, HAQ-DI, patient's global assessment of disease activity, patient's assessment of pain), other secondary outcomes relating to degree of fatigue and general mental and physical health were assessed for each patient.

The degree of anaemia (haemoglobin) and rheumatoid factor (RF) assessment was also included as a secondary endpoint.

Sample size

The sample size was selected based on data from a Phase II dose-finding study (LRO301) in which ACR20 response rates of 60% to 70% were observed in the TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + MTX treatment arms, and a response rate of 40% was observed in the placebo + MTX arm. The response rates in the present study were expected on clinical grounds to be lower than these rates, in view of the relatively treatment refractory patient population being studied. Allowing for 15% of patients in each treatment arm being classified as non-responders because of missing data or early withdrawal and using an alpha level of 0.03 to accommodate for multiplicity, a selected sample size of 150 enrolled patients per treatment group (450 overall) was sufficient to provide 80% power to detect a difference between the proportion of patients achieving ACR20 scores in the TCZ 8 mg/kg + MTX and placebo + MTX treatment arms, assuming that the proportion of patients achieving an ACR20 response would be 50% in the TCZ 8 mg/kg + MTX group and 30% in the placebo + MTX group.

Randomisation

Randomization was administered centrally via an interactive voice response system (IVRS) and was stratified by 'site' using a randomization list provided by Sponsor. A patient's eligibility was evaluated by the investigator to ensure that the inclusion and exclusion criteria were met and that the patient was eligible for participation in the study. Eligible patients were then randomized and assigned a unique randomization number. Medication numbers were assigned by the IVRS prior to dosing at each dosing visit depending on the patient's weight and allocated treatment arm in order to ensure that the correct dosage was provided.

Blinding (masking)

In case of blinding, the study was blinded with the sponsor, investigators, and patients unaware of the treatment assignment of each patient. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment.

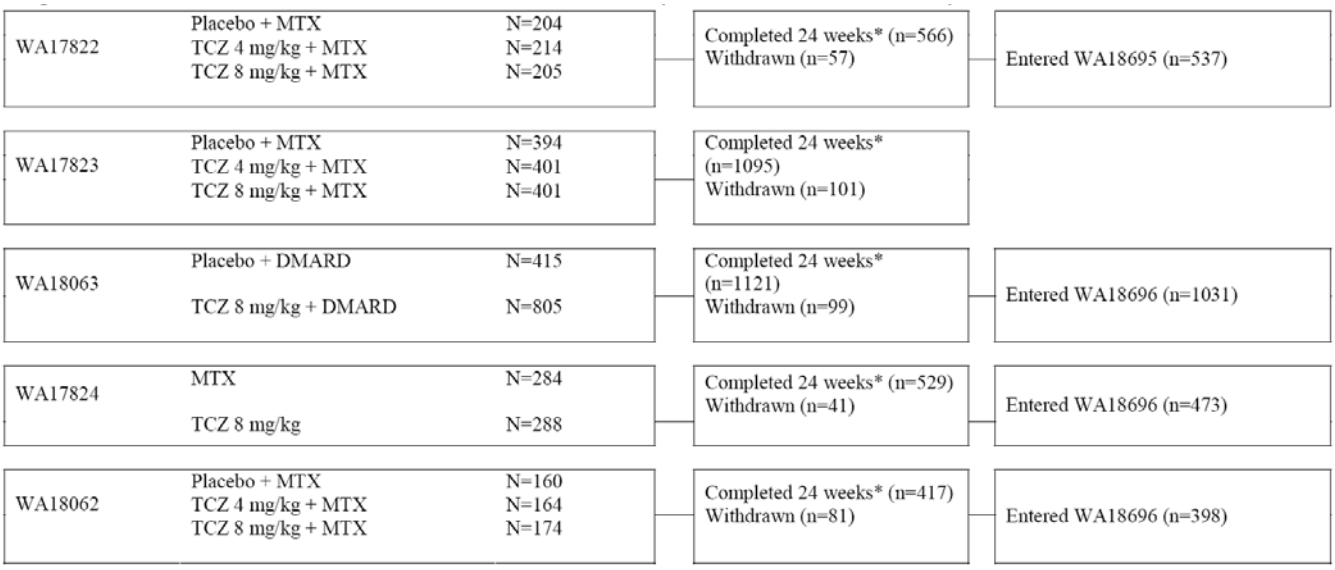
Statistical methods

Statistical methods were appropriate. The approaches taken were appropriately conservative. The intent-to-treat (ITT) population was defined as the primary analysis population for all trials other than WA17824. This study was a non-inferiority trial and the PP population was the primary analysis population, as is standard in studies of this type. Categorical data were analyzed using the Cochran-Mantel Haenszel (CMH) chi-square test, adjusted for site, which is a standard test used for analyses of this type. In addition, the data were analyzed using logistic regression, allowing for the odds ratio to be presented and adjusted for site as well as an assessment of other covariates in the model. The logistic regression analyses provided confirmation of the results using CMH. Appropriate measures for handling of missing data were employed

RESULTS

Participant flow

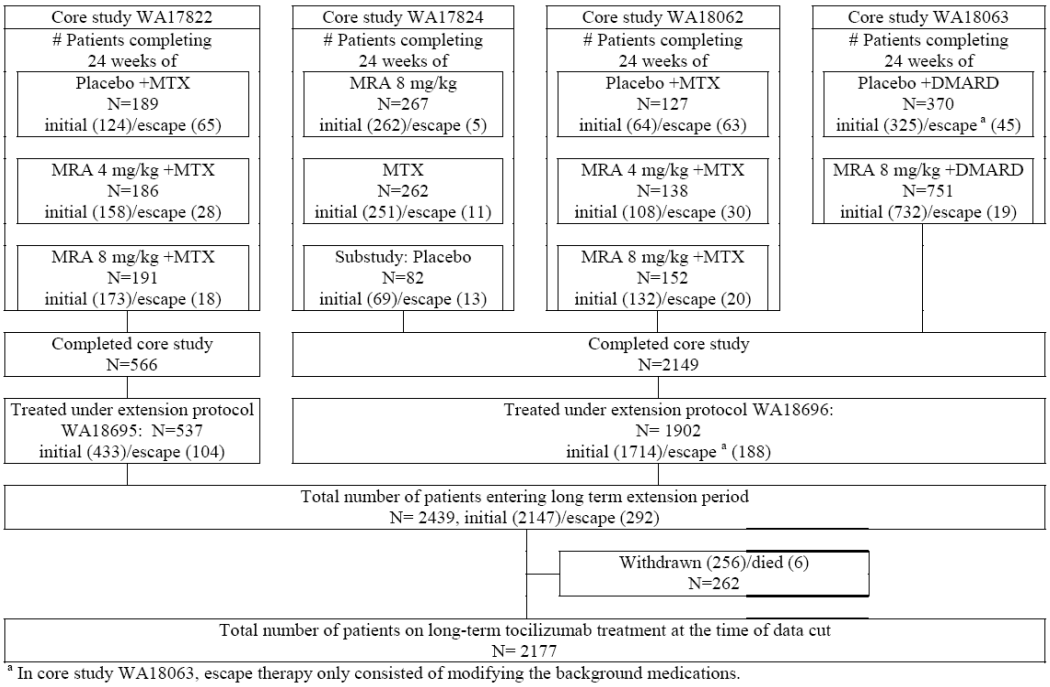
The most important data (Nr. of patients randomized, completed/withdrawn, distribution of patients per arms, etc) of pivotal studies are shown below:



Of the 4211 patients randomized into the TCZ Phase III programme, 4098 received study medication: 1170 (28%) received placebo + DMARD, 774 (18%) received TCZ 4 mg/kg + MTX, 1582 (38%) received TCZ 8 mg/kg + DMARD, 284 patients (7%) received MTX monotherapy, 288 (7%) patients received TCZ 8 mg/kg monotherapy and 101 patients (2%) received 8 weeks of placebo followed by 16 weeks of TCZ 8 mg/kg (placebo / TCZ 8 mg/kg). Table 8 below presents the number of patients in each treatment group, by study.

The disposition of patients in study WA18695/8696 is shown below:

Table 9



[a] In core study WA18063, escape therapy only consisted of modifying the background medications.
Source: STdis_extensum, stex11, STex_coreesc
Numbers of patients in core studies are taken from the core study analyses.

Recruitment

The earliest pivotal study started in 2004, the latest ones in 2005. One was completed in November 2006; all the others in 2007. The extension study started in August 2005 and the cut off date of these ongoing studies was on 20 April 2007.

Conduct of the study

Minor amendments were made in some studies, either not affecting outcomes or statistical analysis or in order to make studies uniform.

Baseline data

For all studies, the treatment groups within each protocol were balanced with respect to demographic and baseline RA characteristics. The study populations were representative of the heterogeneity of characteristics among RA patients with moderate to severe, active disease in terms of the range of disease duration and prior treatments as well as comorbidities and concomitant treatments such as corticosteroids and NSAIDs. Unfortunately the number of DMARD naive patients were only relatively small (129 patients in the MTX group and 115 patients in the TCZ group). (Study WA17824).

Numbers analysed

ITT population is shown in the Table below:

Table 10

	Placebo + DMARD	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + DMARD
WA17822			
No. of Patients Randomized	204	214	205
No. Included in ITT	204	213	205
No. Excluded from ITT	-	1	-
WA17823			
No. of Patients Randomized	394	401	401
No. Included in ITT	393	399	398
No. Excluded from ITT	1	2	3
WA18063			
No. of Patients Randomized	415		805
No. Included in ITT	413		803
No. Excluded from ITT	2		2
WA18062			
No. of patients randomized	161	164	174
No. included in ITT	158	161	170
No. excluded from ITT	3	3	4
WA17824	**Placebo/TCZ**	**MTX**	**TCZ 8 mg/kg**
No. of Patients Randomized	101	284	288
No. Included in ITT	99	284	286
No. Excluded from ITT	2	-	2

When ITT and per-protocol (PP) analysis were compared, no statistically significant differences were observed

Outcomes and estimation

A summary of results of the main studies is given below:

WA17822:

ACR20 (%)

Placebo + MTX (n=204): 26.5%
TCZ 4 mg/kg + MTX (n=213): 47.9%
TCZ 8 mg/kg + MTX (n=205): 58.5%

For both TCZ + MTX groups, there was a highly statistically significant difference from the placebo + MTX group in the proportion of ACR20 responders at week 24 ($p < 0.0001$ for both groups). Similar results were obtained for the ITT robustness and PP population analyses of the primary efficacy parameter. Logistic regression analysis showed that the odds of achieving an ACR20 response at week 24 were 3 times higher for patients receiving TCZ 4 mg/kg + MTX and 6 times higher for patients receiving TCZ 8 mg/kg + MTX than for patients receiving placebo + MTX. ACR20 response rates were higher in the TCZ + MTX groups compared with the placebo + MTX group at all time points from the first scheduled assessment at week 2, with the highest rates being consistently observed in the TCZ 8 mg/kg + MTX group. Secondary endpoint analyses (not shown) supported the primary efficacy findings.

WA17823:

ACR20 (%)

Placebo + MTX (n=393): 27%
TCZ 4 mg/kg + MTX (n=399): 51%
TCZ 8 mg/kg + MTX (n=398): 56%

For the primary endpoint, ACR20 response at week 24 (=interim analysis), significantly more patients in both TCZ + MTX arms compared with the placebo + MTX arm achieved a response ($p < 0.0001$ for both comparisons). Analysis of all secondary endpoints related to disease activity demonstrated significantly better efficacy with TCZ 8 mg/kg + MTX compared with placebo + MTX (data not shown). This included improvements from baseline in all ACR core set parameters (TJC, SJC, pain VAS, CRP, physician global VAS, patient global VAS, Erythrocyte sedimentation rate (ESR), HAQ-DI) as well as the higher clinical hurdle secondary endpoints such as ACR50, ACR70, DAS28 remission and EULAR good' response. Treatment with TCZ 8 mg/kg + MTX was associated with a significant increase in mean haemoglobin levels compared with the placebo + MTX arm, with the most profound effects being observed in anaemic patients. More patients in the placebo + MTX arm compared with the TCZ + MTX arms either withdrew as a result of lack of efficacy or switched to escape therapy due to failure to achieve a > 20% improvement in SJC and TJC.

Evaluation of the inhibition of progression of structural damage was a pre-defined endpoint in study WA17823. The mean change of the total Sharp-Genant Score at week 52 was significantly lower for patients treated with TCZ + MTX (0.34 and 0.29 for the 4 mg/kg and 8 mg/kg groups, respectively) than for patients who received placebo + MTX (1.13, $p < 0.0001$ for both comparisons).

WA17824:

The primary endpoint was the proportion of patients with an ACR20 response at Week 24. The proportion of ACR20 responders at Week 24 was 52.1% in the MTX group and 70.6% in the TCZ group, with a weighted difference of 0.21 (95% CI 0.13 to 0.29). The lower limit of the CI was 0.13. Since the lower limit is greater than –0.12 (pre-defined non-inferiority limit), treatment with TCZ was considered non-inferior to treatment with MTX. As TCZ was shown to be at least non inferior to MTX, further testing for superiority to MTX was conducted. For the purposes of this assessment the ITT population was used. The weighted difference in ACR20 response at Week 24 was 0.19 (95% CI 0.11 to 0.27). Since the lower limit of the 95% CI of the treatment difference was greater than 0, treatment with TCZ 8 mg/kg was demonstrated to be superior to treatment with MTX. This result was highly statistically significant ($p < 0.0001$). To support the conclusions from the primary analysis a comparison was made between all patients treated with TCZ and the placebo treated patients enrolled into the placebo controlled substudy. The ITT population was used for this assessment. As patients in this study received placebo only for the first 8 weeks, this analysis compared proportions of patients achieving an ACR20 response at Week 8. The proportion of ACR20 responders at Week 8 was 13.1% in the placebo/TCZ group and 55.6% in the TCZ group. The weighted difference in ACR20 response at 8 weeks was 0.43 (95% CI 0.34 to 0.52). Since the lower limit of the 95% CI for the weighted difference was greater than 0, TCZ 8 mg/kg is considered to be superior to treatment with placebo at Week 8. In general, all secondary endpoints tested were positive and supported the improved efficacy of TCZ compared with MTX observed with the primary efficacy endpoint. Logistic regression analyses showed the odds of achieving an ACR20 response at Week 24 were approximately 3 times higher in the TCZ group. In addition to the differences observed at Week 24, onset of response occurred earlier in the TCZ group with differences between the two treatment groups apparent as early as Week 2 (ie, first scheduled assessment) for ACR20 response. By Week 2, an increase in mean haemoglobin value of 7 g/l was observed in the TCZ group compared with a mean decrease of 3 g/l in the MTX group.

WA18062:

The proportion of patients achieving ACR20, 50, or 70 responses at Week 24 was consistently higher in TCZ 8 mg/kg + MTX group than the TCZ 4 mg/kg + MTX group or the placebo + MTX group (ACR20: 50% vs 30% and 10%, ACR50: 29% vs 17% and 4%, ACR70: 12% vs 5% and 1%, respectively). In addition, irrespective of the most recently failed anti-TNF medication and the number of previously failed anti-TNF medications, TCZ 8 mg/kg + MTX was shown to be beneficial in this difficult-to-treat

population in all three of these parameters. Similar results were obtained in the PP population analysis and in several sensitivity analyses investigating different methods of imputation for missing data. Logistic regression analysis indicated that the odds of achieving an ACR20 response at Week 24 were 9 times higher for patients receiving TCZ 8 mg/kg + MTX and 4 times higher for patients receiving TCZ 4 mg/kg + MTX than for patients receiving placebo + MTX. Importantly, a statistically significant and clinically meaningful benefit over placebo + MTX was observed in the TCZ 8 mg/kg + MTX group in the higher clinical disease hurdles such as ACR50 and ACR70 response, EULAR 'good' response, and DAS28 remissions rates. In addition to the demonstrated benefits at Week 24, the onset of response occurred early in the TCZ 8 mg/kg + MTX group, with differences from the placebo + MTX group becoming apparent as early as the first scheduled assessment (Week 2). Finally, the benefits of TCZ treatment were reflected in the large numbers of placebo + MTX patients who either withdrew from the study due to insufficient therapeutic response (11%) or entered the escape phase at Week 16 (41%) compared with early withdrawal and escape rates of 2% and 11% for patients receiving TCZ 8 mg/kg + MTX.

WA18063:

The proportion of ACR20 responders at week 24 was 61% (488/803 patients) in the TCZ 8 mg/kg + DMARDs group and 25% (101/413 patients) in the placebo + DMARDs group. For the TCZ 8 mg/kg + DMARDs group, there was a highly statistically significant difference from the placebo + DMARDs group in the proportion of ACR20 responders at week 24 ($p < 0.0001$). Similar results were obtained for the ITT robustness and PP population analyses of the primary efficacy parameter. Logistic regression analysis showed the odds of achieving an ACR20 response at week 24 were 6 times higher for patients receiving TCZ 8 mg/kg + DMARDs than for patients receiving placebo + DMARDs. ACR 20 response rates were higher in the TCZ 8 mg/kg + DMARDs group compared with the placebo + DMARDs group at all time points from the first scheduled assessment at week 2.
Secondary endpoint analyses supported the primary efficacy findings. At week 24, statistically significant differences from the placebo + DMARDs group were achieved for the TCZ 8 mg/kg + DMARDs group for all secondary endpoints related to disease activity. In addition to the differences observed at week 24, onset of response occurred early in the TCZ 8 mg/kg + DMARDs group and differences between the TCZ 8 mg/kg + DMARDs group and the placebo + DMARDs group were apparent by week 2 (ie, the first scheduled assessment). A highly statistically significant increase in haemoglobin was also observed in the TCZ compared with the placebo + DMARDs group. An increase of 6 g/L in mean haemoglobin values in the TCZ 8 mg/kg + DMARDs group was observed early at the first scheduled assessment for haemoglobin at week 2 and mean haemoglobin increase at week 24 was 9.753 g/L in TCZ + 8 mg/kg + DMARDs group vs a mean decrease of 1.280 g/L in placebo + DMARDs group. For the primary and secondary efficacy endpoints at week 24 and throughout the 24-week treatment period, the greatest responses were consistently observed in the TCZ 8 mg/kg + DMARDs group.

WA18695/18696:

At the time of the data cut, the median treatment duration was 41 weeks in the WA17824 group, 52 weeks in the WA18062 group, and 61 weeks in the pooled group. Response rates to therapy with 8 mg/kg TCZ (+DMARD) were generally maintained or continued to improve with duration of treatment. For all efficacy endpoints, the highest response rates were consistently achieved and maintained in the WA17824 group, followed by the pooled group, and then the WA18062 group. However, the pattern of response was similar across all groups, ie, increasing response rate after the first 24 weeks of treatment as well as durability of responses. The very low number of withdrawals due to insufficient therapeutic response (2.4%) supports the observed improvement in efficacy during long-term TCZ treatment. Reported categorical endpoints (ACR20, ACR50, ACR70, ACR90, and EULAR response) were affected by imputation of missing data, as response was generally assessed every 12 weeks, and the study was still ongoing at the data cut. The mean ACRn response increased over time in all 3 study groups and at week 72 reached 48.2 in the WA17824 group, 25.5 in the WA18062 group, and 44.9 in the pooled group. Mean ACR core set parameters and the mean DAS28 showed further improvement after the first 24 weeks of

treatment in all 3 groups. The number of patients who reduced or stopped corticosteroid/DMARD use due to sustained efficacy was 31 and 15 patients, respectively. An improvement in mean haemoglobin level Improvements in RA disease activity were accompanied by an improvement in the patients' quality of life. Results from the SF-36 patient questionnaire demonstrated that both the mean physical and mental component summary scores improved from baseline by more than the minimal clinically important difference. At the week 48 visit, change from baseline in all 8 domains included in the SF-36 score exceeded the minimal clinically important difference in all 3 study groups. The mean Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score increased from baseline and then remained stable for the duration of the studies. A substantial proportion of patients were able to achieve the highest degrees of efficacy indicative of clinical remission or low disease activity.

Ancillary analyses

- Analysis performed across trials (pooled analyses and meta-analysis)

The results from the individual studies provide evidence of the efficacy of TCZ in patients with moderate to severe active RA. However, to provide an estimate of the treatment effect of TCZ in the DMARD inadequate responder patient population and to investigate the effect of TCZ where there are likely to be small differences between the treatment groups, studies WA17822, WA17823 and WA18063 were pooled.

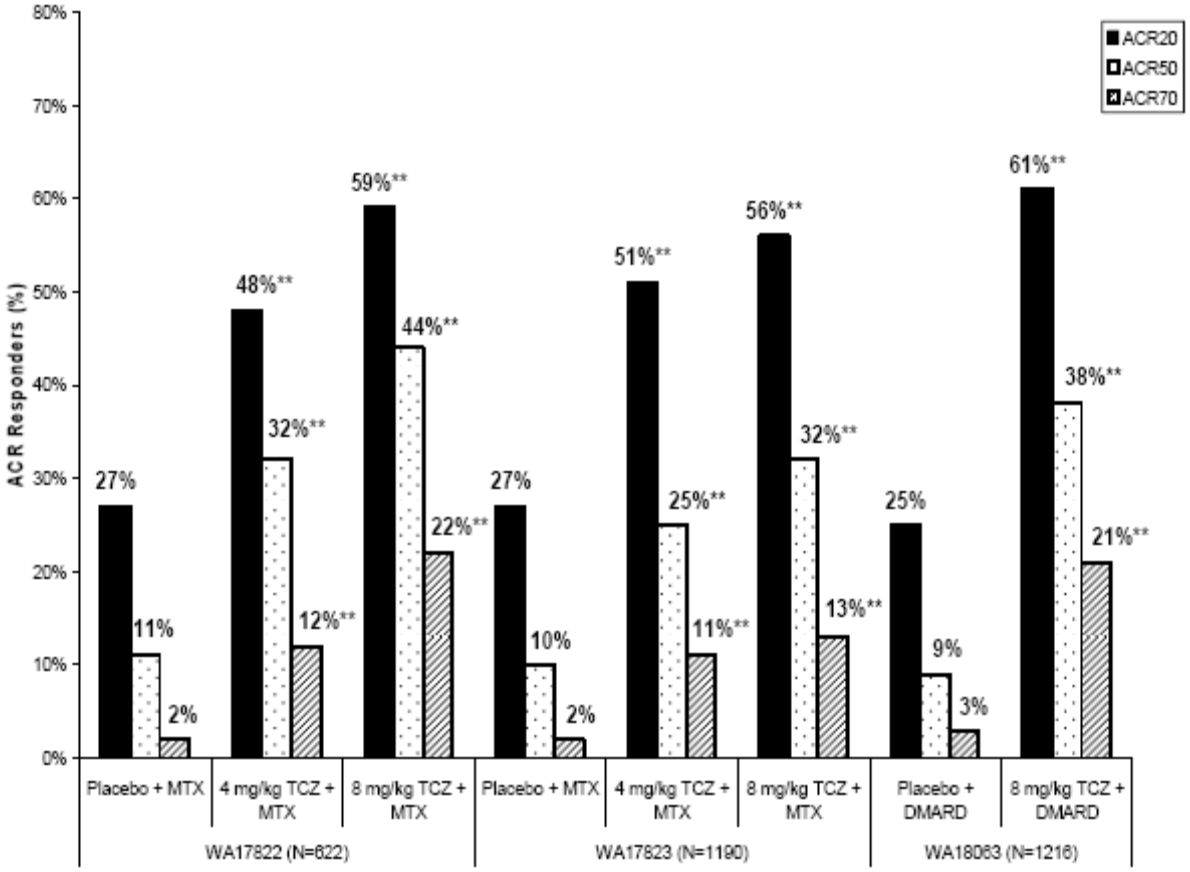
These studies have been considered appropriate to pool based on study design, demographic and baseline characteristics and homogeneity of treatment effect. With this pooling, the results of pivotal studies can be grouped into:
a) DMARD inadequate responders
b) anti-TNF-inadequate responders
c) TCZ monotherapy

The comparison of results of the primary efficacy criteria is shown below:

Table 11

	Pooled DMARD Inadequate Responders N=3028		Anti-TNF Inadequate Responders N=489		Monotherapy* N=570
	TCZ 4 mg/kg + MTX vs placebo + DMARD	TCZ 8mg/kg + DMARD vs placebo + DMARD	TCZ 4 mg/kg + MTX vs placebo + MTX	TCZ 8mg/kg + MTX vs placebo + MTX	TCZ 8 mg/kg vs MTX
ACR20					
Odds ratio	2.897	4.124	3.956	9.070	2.812
95% CI	(2.316, 3.624)	(3.450, 4.930)	(2.131, 7.342)	(4.976, 16.534)	(1.824, 4.335)
p-value	<0.0001	<0.0001	<0.0001	<0.0001	-
ACR50					
Odds ratio	3.567	5.532	5.075	10.449	1.959
95% CI	(2.678, 4.751)	(4.360, 7.019)	(2.027, 12.708)	(4.315, 25.307)	(1.286, 2.983)
p-value	<0.0001	<0.0001	0.0005	<0.0001	-
ACR70					
Odds ratio	6.138	8.897	4.012	11.012	3.009
95% CI	(3.751, 10.045)	(5.796, 13.658)	(0.838, 19.219)	(2.536, 47.810)	(1.818, 4.981)
p-value	<0.0001	<0.0001	0.0822	0.0014	-

Figure 5: Proportion of ACR20, ACR50 and ACR70 responders at week 24 for studies WA17822 (inadequate MTX responders), WA17823 (inadequate MTX responders) and WA18063 (inadequate DMARD responders)



* $p < 0.01$, TCZ vs. placebo + MTX/DMARD
** $p < 0.0001$, TCZ vs. placebo + MTX/DMARD

- Clinical studies in special populations

Of the various groups (children, elderly, gender, race and weight/BMI), only body weight (BW) has an impact upon PK of TCZ. There was a slight decrease in clinical efficacy among patients with body weight over 100 kg. However, a logistic regression model failed to show any significant differences between treatment subgroups.

- Supportive studies

Joint Damage Study **MRA012JP**: At the time of this submission, there are no radiographic data from the pivotal studies. However, data showing the effects of TCZ on inhibiting structural joint damage, bone densitometry and markers of bone metabolism are available from a supportive study, MRA012JP, in Japanese patients from the Chugai development program.

This was a multi-centre, parallel group, open-label study conducted at 26 centres in Japan in RA patients who had an inadequate response to current DMARD or immunosuppressive therapy. Patients were randomized to remain on existing DMARD or immunosuppressant treatment or TCZ 8 mg/kg iv every 4

weeks for 52 weeks. In the control group, the concomitant use of drugs that slow bone or joint destruction (eg, infliximab, etanercept, leflunomide) was prohibited. No restrictions were placed on switching DMARDs or the doses of DMARDs and immunosuppressants for treating RA from the first observations onwards. The primary endpoint was the change in erosion score at week 52, according to the modified Total Sharp Score methodology of radiograph reading. Radiographs were scored by two blinded independent readers using the van der Heijde modified Sharp method. The time course of absolute change in lumbar and femoral bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) at weeks 28 and 52 was assessed as a secondary endpoint. The treatment groups were generally well-balanced with respect to baseline demographic and disease characteristics. The mean duration of RA was 2.4 years in the control group and 2.2 years in the TCZ group. Mean baseline DAS28 scores were 6.4 in the control group and 6.5 in the TCZ group. Mean baseline Total Sharp Scores were 30.6 and 28.3 in the control and TCZ groups, respectively, and the rate of annual progression was 12.3/year in the control group and 14.1/year in the TCZ group. At week 52, the TCZ group had statistically significantly less radiographic change in Total Sharp Score, Erosion Score and Joint Space Narrowing compared with the control group. Additionally, there were significant differences between the treatment groups in changes in serum osteocalcin (marker of bone formation), urinary deoxypyridinoline (marker of bone resorption) and lumbar and femoral BMD. TCZ treatment prevented bone loss with a significant increase in serum osteocalcin levels, significant decrease in deoxypyridinoline levels and a smaller decrease in lumbar and femoral BMD compared with conventional DMARD treatment.

These results provide evidence to support the hypothesis that inhibition of IL-6 by TCZ may have beneficial effects in slowing bone and joint destruction.

Table 12 Change in Radiographic Scores (Full Analysis Set)

	Control Group N=143	Tocilizumab 8 mg/kg N=157	P-value*
Week 28			
Total Sharp Score			
Mean (95% CI)	4.5 (3.1, 6.0)	1.9 (1.2, 2.6)	p<0.05
Median (IQR)	1.0 (0.0, 5.0)	0.5 (0.0, 2.0)	
Erosion Score			
Mean (95% CI)	2.4 (1.6, 3.2)	0.8 (0.4, 1.2)	p<0.01
Median (IQR)	0.5 (0.0, 2.5)	0.0 (0.0, 1.0)	
Joint Space Narrowing Score			
Mean (95% CI)	2.2 (1.4, 2.9)	1.1 (0.7, 1.6)	NS
Median (IQR)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	
Week 52			
Total Sharp Score			
Mean (95% CI)	6.1 (4.2, 8.0)	2.3 (1.5, 3.2)	p<0.01
Median (IQR)	2.5 (0.0, 7.0)	0.5 (0.0, 3.0)	
Erosion Score			
Mean (95% CI)	3.2 (2.1, 4.3)	0.9 (0.3, 1.4)	p<0.001
Median (IQR)	1. (0.0, 3.5)	0.0 (0.0, 1.0)	
Joint Space Narrowing Score			
Mean (95% CI)	2.9 (2.0, 3.8)	1.5 (0.9, 2.1)	p<0.05
Median (IQR)	1.0 (0.0, 4.0)	0.0 (0.0, 1.7)	

IQR = interquartile range; NS = not significant

* P values were analyzed with a rank transformed analysis of covariance (ANCOVA) on the change scores that included factors for baseline score and baseline disease duration

Study **MRA213JP** was a Phase III, two-arm, parallel-group, double-blind, multicentre study comparing TCZ 8 mg/kg monotherapy every 4 weeks with MTX 8 mg weekly in RA patients with an inadequate response to MTX. The study was designed to assess safety and signs and symptoms of RA after 24 weeks of TCZ therapy.

Clinical safety

The pivotal clinical safety data supporting this application derives from five adequate and well-controlled, double blind, international, Phase III studies in adult patients with RA: WA17822, WA17823, WA17824, WA18062 and WA18063.

These 5 studies are referred to as the core studies and were conducted by Roche. The core studies are completed, with the exception of the ongoing 2-year study WA17823, for which only pre-planned 24-week interim data are included in this submission. Long term safety information from 2439 RA patients treated with open-label TCZ 8 mg/kg was also provided. The data are derived from 2 open-label ongoing extension studies (cut off date April 20th, 2007). The duration of the extension studies will be 5 years.

Additional information is available from studies conducted by the applicant/sponsor's co-development partner, Chugai Pharmaceutical in healthy volunteers, PK studies in RA patients, RA patients who had inadequate response to DMARDs or MTX and 6 studies in Castleman's Disease (121 pts.), 1 in Crohn's (24 pts), 3 in multiple myeloma (37 pts.) and 1 in systemic lupus erythematosus (14 pts).

- Patient exposure

The trials represent a broad range of both of RA patients and other auto-immune conditions. The RA patients include those with early disease (<2 years), MTX-naïve patients, partial responders to standard non-biologic DMARDs, and those who had failed treatment with anti-tumour necrosis factor (TNF) agents.

The core safety data set encompasses TCZ when used alone or in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) for reducing signs and symptoms in adult patients with moderate to severe active RA. For the proposed posology (8 mg/kg every 4 weeks) and indications data have been collected in 1870 patients for 6 months.

Long-term safety analyses were based on all patients who completed the 24-week controlled studies and received TCZ in the open-label extension studies. A total of 2439 patients completed the core studies and entered the extension studies providing, 2188/2439 patients (89.7%) had been receiving TCZ treatment for at least 24 weeks, 1507 patients (61.8%) had been receiving TCZ treatment for at least 48 weeks and 574 patients (24%) for at least 18 months. The mean and median extent of exposure to TCZ treatment from the first dose was 1.08 years.

Taken together, this represents an acceptable safety database, both in number of patients and exposure time with TCZ. Upon request the applicant provided a tabular overview showing 6, 12, 18, month data for the number of patients belonging to the proposed target population at the proposed dose (8 mg/kg) and proposed SPC indications, i.e. stratified by prior therapy and concomitant treatment, thereby giving exact numbers and duration for each proposed indication.

Table 13: Exposure to Tocilizumab 8 mg/kg Every Four Weeks by Patient Population

Moderate to Severe RA	Monotherapy			Combination therapy					
				MTX			DMARD		
	6M	12M	18M	6M	12M	18M	6M	12M	18M
Not previously treated with DMARDs[1]									
No. of Patients	132	94	52				118	48	14
Patient years exposure	161.4	137.6	87.8				110.4	59.8	21.9
Inadequate response to DMARDs									
No. of Patients[2]	182	124	66				177	96	34
Patient years exposure	214.6	180.8	112.5				172.1	118.2	50.3
Non Escape[3]									
No. of Patients	-	-	-	1295	880	646	453	382	270
Patient years exposure				1672.8	1452.3	1180.9	661.8	613.1	481.5
Escape[4]									
No. of Patients	-	-	-	135	95	80	-	-	-
Patient years exposure				180.3	160.6	142.2			
Inadequate response to anti-TNF									
Non escape patients[5]									
No. of Patients	-	-	-	277	215	125	-	-	-
Patient years exposure				356.5	313.1	207.9			
Escape patients[6]									
No. of Patients	-	-	-	101	76	41	-	-	-
Patient years exposure				124.1	105.9	65.7			

1. WA17824: patients were permitted to add DMARDs in the extension. Exposure on monotherapy is summarised separately from combination therapy
2. Patients from WA17824 who were not DMARD-naïve at baseline;
3. WA17822, WA17823 (6 month data only) and WA18063: patients who did not receive escape therapy during the studies. WA18063: a wide range of DMARDs were permitted as background therapy whereas other studies have MTX-only background medication Thus, exposure data from WA18063 separates MTX only (shown in MTX combination therapy columns) and other background therapies excluding MTX alone (shown in DMARD combination columns). Patients taking ≥ 2 background DMARDs including MTX are included in the combination column. Patients who switched DMARD treatments are counted in the original active treatment group actually received, i.e. if they were on MTX alone in the core study and increased to ≥ 2 DMARDs in the extension study, they are included in the MTX-only group.
4. Patients from WA17822 and WA17823 who received escape therapy In WA18063, no's on escape not included as escape was increase in DMARDs, not switch to TCZ.
5. Patients from WA18062 who did not take escape therapy
6. Patients from WA18062 who received escape therapy

Additional 4 month safety data update (4MSU)

A 4 month update of the safety information was provided from the open label extension studies WA18695 and WA18696, (cut-off date of October 1, 2007).

An update was also provided on deaths and SAEs occurring from September 1, 2007 to January 31, 2008, in the following:

- The ongoing Japanese development programme (including non-RA indications);
- Spontaneous reports from the treatment of multicentric Castleman's Disease;
- Compassionate use of TCZ in children with systemic onset inflammatory juvenile arthritis;
- The ongoing study WA17823; and
- The ongoing studies WA18695 and WA18696 (beyond October 1, 2007).

Data was also included regarding the safety and efficacy of TCZ 8 mg/kg monotherapy from patients in study WA17824 who achieved a ≥ 50% decrease in the number of active swollen and tender joints (assessed from baseline) and opted to continue blinded treatment in the so-called "transition phase".

Further information was submitted from the immunogenicity testing program including data from patients during the first 6 months of WA17823 and long-term follow-up of patients in WA18695 and WA18696.

By October 1, 2007, an additional 123 patients had entered study WA18696, providing a total of 2562 patients who received at least one dose of TCZ in the long-term studies. Of the additional 123 patients who were included in the 4MSU population, 93 were from the "transition phase" of WA17824.

The data was compared to the existing long-term data from the studies WA18695 and WA18696 in 2439 patients and AEs of special interest (infections, infusion reactions, cardio-vascular AEs, neoplasms, gastrointestinal (GI) ulcerations and perforations, skin AEs, blood and lymphatic AEs, hepatic AEs, autoimmune events and demyelinating disorders, and fractures) were focused on.

The 4 MSU population showed a ~ 3-5% increase in severe AEs, related AEs, serious AEs and AEs leading to dose modification compared to the initial application. This may have to do with the relatively short time period addressed in this report (30th April 2007 – 1st Oct. 2007) or may indicate a trend. Any tendencies of increases would have to be captured by the RMP. In general the types of AEs observed in the 4MSU population were similar to those reported previously. The new events (3x cutaneous lesions of discoid lupus, and 1x arteritis, hypertensive encephalopathy, ischemic colitis, intestinal obstruction, hepatic fibrosis, pulmonary hypertension, glioblastoma and B cell lymphoma) should be kept in mind for the evaluations of the PSURs.

In the long-term studies the development of HAHAs (2.3%) neutralizing antibodies (<1%) was low. The increased exposure to TCZ did not appear to result in an increase in the proportion of patients who developed anti-TCZ HAHA and had associated allergic events. However, it remains uncertain as to how the methods and assay for determining HAHAs affected the outcome (see also RMP)

- Adverse events

Overall, adverse effects associated with the mechanism of IL-6R inhibition were observed in all TCZ treatment groups. The safety profile in the 5 core studies was fairly consistent (also between the 4 and 8 mg/kg dosing regimens) and the following main safety signals emerged:

Infections

IL6 is a pleiotropic 24 kDa cytokine influencing antigen-specific immune responses and inflammatory reactions. It is one of the major physiological mediators of acute phase reaction. As pathogenic bacterial lipoproteins and lipopolysaccharides stimulate the production of IL-6 and sIL-6R, which then act on multiple cell types to activate the 'innate' immune response, tocilizumab would be expected to have an immunosuppressive effect on the development of effective immunity to bacterial and viral infections.

In the studies, the TCZ-combination therapy treated patients had higher rates of infection compared to the placebo patients, more patients with 2 or more infections, more severe infections and more serious infections (placebo: 1.5% vs TCZ 2.1%). Within the category of infections, respiratory infections, skin

infections and GI were predominant. Systemic infections were rare (3 events of sepsis). The nature of the serious infections in 2644 TCZ-treated patients in the controlled trials were pneumonia (0.5%), cellulitis (0.3%), and herpes zoster (0.2%), sepsis (0.1%), gastroenteritis (0.1%). Opportunistic infections were isolated cases (Pneumocystis carinii, Mycobacterium avium intracellulare), and in the ongoing Japanese studies intracellular or opportunistic infections included 2 cases of tuberculosis (TB), one case of bronchopulmonary aspergillosis and one case of candida osteomyelitis.

A higher incidence of infections was observed in patients who were previously exposed to anti-TNF medications in all treatment groups in study WA18062 compared with patients in the other studies.
Cellulitis was questionably observed more frequently in the TCZ compared to the control groups and the applicant had been requested to clarify this issue. Although there is an overlap of the 95% CI between the placebo and bapineuzumab groups for cellulitis, it cannot thus necessarily be attributed to TCZ, the sponsor has nevertheless included cellulitis in the list of adverse reactions in the SPC, in recognition of the increased risk of infections in patients treated with TCZ.

As IL-6 is known to differentiate B cells into antibody-producing plasma cells the concern was raised that by blocking IL-6, one may expect a decrease also in B cell functions and hence IgG levels and antigen-specific antibodies (such as anti-pneumococcal-antibody titres/anti-tetanus titres) The sponsor committed to continue monitoring the levels of immunoglobulins in the ongoing open label extension studies and to conducting an additional vaccination study as a part of ongoing open-label long-term extension study.

The timely detection of serious infection may be difficult due to the suppression of the acute phase reaction (CRP, neutrophils). This aspect has been included in the SPC.

Gastrointestinal disorders
In the TCZ preclinical programme, no signals of GI toxicity were observed. However, in healthy volunteers, events of diarrhoea, mouth ulceration, vomiting, abdominal pain, gingival pain, oral pain and flatulence were reported. Although the wide use of corticosteroids and NSAIDs in patients with RA contributes to these side-effects, gastric disorders (mainly gastritis and upper GI ulcers) were observed more frequently with TCZ combination treatment compared with the control. In one study (17824) related GI AEs in the monotherapy TCZ 8 mg/kg group(~20%) were the same as the MTX monotherapy group, but practically double that of the combination therapy TCZ + MTX (9%) and quadruple that of MTX + placebo in another study (17823; 5%). The discrepancies between the studies were thought to be due to the different focusing of the patient in the Informed Consent Form. In 5 cases the increased inflammation led to perforations and in 2 cases to death. The rate of total GI perforations is 0.184 /100 pt-years which is slightly higher than that reported in the literature for RA patients. Gastritis, mouth ulceration, diverticulitis and its complications (peritonitis, perforation, fistulae and abscess) are listed as adverse reactions in the SPC.

Infusion reactions
Infusion reactions occurred mainly during the first or second infusion. In the monotherapy groups, 6% in the TCZ 8 mg/kg group and 2% in the MTX group had infusion reactions. In the combination therapy groups ~5% in the TCZ groups and 3% in the placebo groups had infusion reactions. In the long term safety population, these defined events were reported by 6.5% of patients. Infusion reactions comprised mostly hypertension, rash and pruritus. Overall, 12 patients experienced medically significant hypersensitivity reactions (six anaphylactic reactions).

Skin disorders
There was no evidence of skin toxicity with TCZ from preclinical data. Single events of rash were reported in studies in healthy volunteers. Therefore the clinical data with increased skin and subcutaneous tissue disorders raise a new concern. More skin disorders (rash, dermatitis and pruritus, skin ulcers) occurred in the TCZ groups. No clear connection could be seen in the patients who had higher eosinophils. Skin related AEs occurred independently of dose level (for skin cancer, see next paragraph on malignancies).

Malignancies

Malignancies are increased in patients with RA and additionally with some treatments commonly used in RA (MTX and DMARDs). The risk appears to be particularly higher for lymphoproliferative malignancies, such as non-Hodgkin's lymphoma and multiple myeloma, in RA patients compared with the general population.

IL-6 is recognized as a potent growth factor in the pathogenesis of some forms of cancers; in non-clinical TCZ pharmacology studies anti-proliferative effects were observed. However, IL-6 also is claimed to have a role as a therapeutic anti-tumour agent. Thus, it remains to be seen what long-term effects TCZ will have in tumorigenesis.

Overall the malignancies did not seem to be increased compared to the placebo groups. For solid cancers it was slightly lower than the MTX group. Non-melanoma skin cancers in the TCZ groups were 0.4/100pt-y – 0.71/100 pt-y (placebo 0.6/100 pt-y). In the overall clinical trials (including long-term data) the rate of malignancies is 1.27/100 pt-y, this may indicate an increase. The 4/5 thyroid neoplasms were shown to be benign in character (one patient was lost to follow-up).
The SPC text on malignancies refers to the pre-clinical data and now includes a section on the limited clinical data to date. Long-term safety evaluations are ongoing.

Cardio/vascular disorders

In the monotherapy groups, 2 patients (0.7%) in the TCZ 8 mg/kg group had coronary events and none were reported in the MTX group, in the combination therapy TCZ and placebo group rates were similar (0.6% and 0.5%). In the long-term safety population, 14 patients had serious coronary ischemic events. The rate of myocardial infarction in patients treated with TCZ during the Phase III studies was 0.35 per 100 patient years of exposure. The observed rate of myocardial infarction with TCZ is within the rates reported in literature for myocardial infarction in patients with RA (0.4 – 0.7/100 pt-years).
Premature cardiovascular disease is a feature of extra-articular RA, leading to an increased risk for myocardial infarctions, heart failure and cerebrovascular disease. In the studies, vascular disorders (mainly hypertension) occurred with up to double the frequency in the TCZ group *vs* the control groups. In addition¸ lipid parameters are increased in all TCZ groups, in some studies there is also an increase in atherogenic indices. Viewed long-term, the RA population may thus be at an increased risk for ischemic events (in addition to the underlying risk). As the 6 month data is relatively short, it is momentarily difficult to come to a clear conclusion with regard to ischemic events. Post-authorisation the applicant will be entering the treated patients into registries where data on this aspect will be obtainable. The sponsor commits to track ischaemic events in registry studies and will submit annual reports to the EMEA. The role of TCZ as a possible trigger to either a pre-existing cardiac/ cerebrovascular history or to a medication known to increase the risk of vascular events is difficult to assess. In the updated Risk Management Plan the sponsor has initiated a dedicated study to assess the effect of TCZ on surrogate markers of atherosclerosis.

Nervous system and psychiatric disorders

Nervous system disorders were experienced more frequently in the TCZ groups compared to the control groups. The most common events were headache and dizziness. The rate of cerebrovascular accident events in patients treated with TCZ during the Phase III studies was 0.26 per 100 patient years of exposure. This is slightly lower than rates reported in the literature for the RA adult population (~0.5 /100 pt-years).

Two events suggestive of central demyelination reported in the original submission were enrolled in clinical trials WA17823 and WA18696 (extension of WA18062). After completion of the original application dossier, the sponsor received a report of a case of leukoencephalopathy (patient 114002) in open-label, long-term extension study MRA215JP in RA in Japan. The extensive work-up of the case showed that a drug related encephalopathy could not be ruled out by exclusion. However, the PCR testing for the JC virus in the spinal fluid was negative on three occasions, thereby making the possibility of PML very unlikely.

Further investigation revealed three neurological events of interest: cranial neuropathy, abnormal nuclear magnetic resonance imaging and peripheral demyelination. The applicant has modified the RMP and the SPC to incorporate this potential adverse event

Although the monotherapy TCZ group shows slightly higher percentages of patients with insomnia, anxiety and depression, the overall TCZ group does not show an increase compared to the placebo DMARD group, thus an inclusion in the SPC is not necessarily warranted.

Eye disorders

Eye disorders were reported more frequently in the TCZ groups; the difference being mainly due to conjunctivitis (2.75 in the all TCZ group vs. 1.77 in DMARD+ placebo/r 100 patient-years). However, the confidence intervals for all TCZ groups overlapped with the placebo + DMARD group, showing that there were no significant differences between TCZ and control. However, recognizing the increased risk of infections in patients treated with TCZ, conjunctivitis has been included in the list of adverse reactions terms in the SPC.

Swelling / edema

The diverse nature of oedema makes it difficult to assess. Although the TCZ 8 mg/kg + DMARD group was higher compared to placebo + DMARD (5.84 vs. 3.75, respectively), the overlapping confidence intervals do not allow to draw any precise conclusion.

The 6-month data for angioedema revealed 17/2644 (0.64%) cases in the TCZ group and 3/1170 (0.25%) in the placebo group. In the TCZ 8mg/kg groups (SPC recommended dose), there are 16/1870 (0.85%) and in the all-exposure TCZ population there are 33/3778 (0.87%) cases of angioedema, indicating that there may be a trend. The sponsor has proposed to include the evaluation of risk of angioedema as part of the evaluation of serious hypersensitivity reactions. This will encompass reporting of angioedema events by means of guided questionnaires (see RMP; post-marketing reports) and detailed evaluation of angioedema events in the ongoing clinical trials

Other biological agents and risks

Clinical experience both in RA and a number of other autoimmune diseases has been gathered with other biological medicinal agents that block TNF activity. The main safety concerns include serious infections (TB), infusion-related reactions, antibody development, worsening of cardiac disorders, neurological disorders, blood disorders, and possible increased risk of malignancies. These safety concerns remain after a patient has been switched to TCZ combination therapy.

Bone function

IL-6 stimulates osteoclast activity and bone resorption. By inhibiting this activity through exposure to TCZ (preclinical data) normal bone function may possibly be maintained and thus not deemed to be a risk factor. Nevertheless, fractures were addressed separately in the studies. In addition, approximately 50% of patients with fractures were taking oral steroids at baseline and approximately 60% of them had a history of osteopenia/osteoporosis and the majority of those patients with a history were on bisphosphonates.

Excipient:sucrose

Sucrose has been thought to cause or enhance the development of acute renal failure (ARF) when administered in larger amounts e.g. in some sucrose-containing intravenous immunoglobulins (IVIG) esp. in the presence of pre-existing renal insufficiency, creatinine > 1.5 mg/dl and concomitant nephrotoxic drugs. The content of sucrose in the TCZ formulation is 50 mg/ml (or 2.5 mg sucrose/1 mg TCZ). Therefore administration of TCZ 8 mg/kg every 4 weeks corresponds to a sucrose uptake of 0.02 g/kg every 4 weeks. For sucrose-containing IVIGs the sucrose load would be considerably higher, namely ~0.35 – 1.67 g/kg. Nevertheless it is not known precisely in patients with pre-existing renal conditions what the minimal amount of sucrose is that might trigger further damage. In older preclinical literature a single 0.05 mg sucrose infusion was sufficient to cause renal damage with tubular swelling in healthy dogs. One 71 year-old patient died (in study WA18063) of cardiopulmonary arrest secondary to end stage renal failure after having elevated renal function tests throughout the study (9 TCZ infusions). He was diagnosed with an obstructive uropathy with

secondary renal insufficiency. The death was considered by the investigator to be unrelated to study drug. However, the SPC should reflect that additional caution should be exercised in patients with pre-existing renal conditions

- Serious adverse event/deaths/other significant events

The general pattern of serious adverse events was similar in nature to the adverse events listed above. The most common serious adverse events in all treatment groups were infections. Serious infections were reported with a higher frequency in all TCZ 8 mg/kg groups compared with their respective controls, and compared with the TCZ 4 mg/kg + MTX arm. Few infections led to withdrawal (< 1%), and similar proportions of patients withdrew because of infections in each TCZ treatment group. Most patients with serious infection temporarily interrupted or reduced dosing.

By the April 20th, 2007 cut-off date, a total of 26 deaths were reported in all studies conducted in the RA indication, which enrolled 6315 patients. Twenty-one of these deaths were reported in the Roche clinical trial programme, which had 4098 patients in the safety population In the 6 month controlled clinical studies, the rate of deaths was similar in TCZ treated patients compared with control groups (0.41 per 100 patient years exposure in the pooled TCZ groups vs 0.8 per 100 patient years exposure in the placebo + DMARD group and 0.75 per 100 patient years exposure in the MTX group. The rate of deaths did not increase in long term extension studies (0.42 per 100 patient years exposure).

In the core 24-week studies 5 deaths occurred in patients receiving treatment with the TCZ 8 mg/kg dose, two of these (2/1582 [0.13%]) occurred in patients enrolled in trials comparing the 8 mg/kg and 4 mg/kg dose regimens and three occurred in trials evaluating the 8 mg/kg dose alone. Causes of death in the TCZ patients were myocardial ischemia, cardiopulmonary arrest, stroke, postoperative infection, GI haemorrhage. Five deaths occurred in the control groups during the 6-month double-blind period due to pneumonia, Wegener's granulomatosis, coronary artery thrombosis and intestinal obstruction in the placebo + DMARD group and due to lung cancer in the MTX group.

An additional 11 patients died during treatment in the long-term safety analysis, 5 of them due to infections. In the other patients the causes of death were myocardial infarction (2 patients), cancer, suicide, progressive idiopathic neuropathy (one patient each), and in one patient the cause of death is unknown.

Two additional patient deaths occurred following the cut-off date for reporting data in the clinical safety summary (1x acute myocardial infarction 8 months after completion of the core study (WA17822) while awaiting transition to the long-term extension study; 1x cardiopulmonary arrest during the long-term extension study)

- Laboratory findings

<u>Neutrophils</u>
Decreases in neutrophil counts without associated decreases in other haematology laboratory parameters have been reported in animal studies. This was seen in the clinical studies in healthy volunteers and in patients with RA and was felt to constitute a pharmacodynamic effect.

From the submitted data, decreases in neutrophil counts were recorded more frequently in the TCZ groups mainly with shifts in CTC grade from normal to -1. These were observed after the first dose of treatment and were sustained throughout the dosing interval. There was little to no clear temporal association between low neutrophil counts and the occurrence of infections. In patients with infections, approximately one-third of infection AEs were associated with an increase of neutrophils, one-third with a decrease, and approximately one-third did not change. The pattern of these changes was similar in both treatment groups. Severe decreases in neutrophil count to < 0.5 x 109/L were infrequent (8 patients in the combination therapy studies and 4 patients in the long-term safety analysis) and led to discontinuation of TCZ after which the neutrophil counts returned to pre-treatment values. Neutropenia as an AE was not reported in the placebo or MTX groups, but in up to 1.4% in the

TCZ groups. There also seems to be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. This has been added to the SPC.

Platelets
A decrease in the formerly slightly elevated platelet count to within the normal range was observed in all the TCZ groups with only isolated incidences of thrombocytopenia (as an AE it occurred in 0.1-0.3% in the 6 month data). The SPC has been revised to include wording relating to monitoring of platelets, as well as reference to the occurrence of rare cases of grade 3-4 thrombocytopenia.

Hepatic transaminase elevations
As there was no evidence of increases of hepatic transaminases in the pre-clinical toxicology studies or in the healthy volunteers, the clinical data raise a new concern. In addition, *in vitro* studies conducted with TCZ on human hepatoma cell lines have however not been able to clarify this clinical finding.

The applicant suggested that these effects in humans are related to the combined effects of concomitant medications (MTX, leflunomide, NSAIDs), as well as concomitant conditions (obesity, diabetes, metabolic syndrome) and thus may influence liver function in patients with RA. However, the exact cause is unclear and not fully elucidated.

In the studies elevations in liver function tests were more frequent in the TCZ groups compared to placebo groups, but slightly less frequent in the monotherapy compared to MTX. The applicant stresses that these elevations were single events; however, this could not be extracted from the data which showed prevailing percentages of patients with increases through Week 24. In general these elevations were managed by simple or no intervention. ALT + AST elevations were not associated with simultaneous elevations of bilirubin. However, bilirubin alone was also more frequently increased in TCZ patients compared to placebo patients. Patients were required to discontinue PP when elevations reached > 5 ULN. In some cases there was evidence of steatosis. Only one biopsy was performed showing a fatty liver.

The aspect of increases of hepatic enzymes is addressed in the SPC, as are the necessary dose adjustments in case of laboratory abnormalities.

Lipid parameters
IL6 has also been implicated in regulating adipose mass. However, no effect of TCZ on lipid parameters was seen healthy volunteers or in animal studies.

Patients with chronic inflammatory conditions, such as active RA, have lower lipid levels in comparison with the general population and an increase in lipid parameters has been associated with other biological agents such as anti-TNFs. An increase in lipids by TCZ may thus reflect the pharmacodynamic effect of TCZ on suppression of inflammation in patients with RA. However, such increases could pose a long-term risk for the development of atherosclerosis and subsequently of cardiovascular/cerebrovascular incidents.

Elevations in lipid parameters and atherogenic indices were more frequent in patients on TCZ compared to control groups. These elevations occurred early after initiation of treatment and stabilized on continuation. They were associated with decreases in CRP and other acute phase proteins. There did not seem to be a direct association with the occurrence of cardiovascular events, however, 6 month data would not really suffice to assess this risk. In addition, under TCZ treatment hypertension and in some cases cardiac events were increased. Thus, the long-term effect of increased lipids and atherogenic indices in this chronically ill patient population remains to be seen. Elevations in total cholesterol generally responded to treatment with lipid-lowering agents. This aspect is addressed in the SPC.

Immunogenicity HAHAs)
Tocilizumab was produced by selecting a mouse anti-human IL-6R monoclonal antibody with the most potent inhibitory activity in an *in vivo* nude mouse myeloma cell xenograft system.

Humanization was performed by grafting the Complementarity determining region (CDR) of the mouse anti-human IL-6R monoclonal antibody onto a human IgG1 antibody framework, followed by transfection of both light and heavy chain genes into CHO cells to produce a humanized antibody.
A total of 2876 patients have been tested for anti-tocilizumab antibodies in the controlled clinical trials. Forty-six patients (1.6%) developed positive anti-tocilizumab antibodies, of whom 5 had an associated medically significant hypersensitivity reaction leading to withdrawal. In 30 patients (1.1%) who developed neutralizing antibodies, no apparent correlation to clinical response was observed.

- Safety in special populations

Elderly: The only difference, i.e. higher frequency of serious infections in older patients does not seem to be related directly to the TCZ treatment and may rather due to the disease- (RA) and age-related co-morbidities.

- Safety related to drug-drug interactions and other interactions

CYP-450
IL-6 has been shown to cause depression of major P-450 (CYP)-associated drug metabolism in humans during inflammation, infection and possibly in other disease indications including cancer. Thus, the possibility cannot be ruled out that treatment with tocilizumab may promote the metabolism of CYP-metabolized drugs. This is reflected in the SPC.

- Discontinuation due to adverse events

The withdrawal of patients due to safety reasons occurred infrequently and was more prominent in the combination therapy (TCZ 8 mg/kg + DMARD) group. The most common types of AEs leading to discontinuation were abnormalities of liver function tests and infections. There was no indication that any particular types of events within any of the MedDRA SOCs led to an increase in withdrawals.

- Post marketing experience

No post-marketing experience has been available at time of Marketing Authorisation.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 14: Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Identified risks		
Serious infections	• Routine pharmacovigilance • Special CRF for events of special interest: implemented in clinical trials as of Q4 2007/Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board Epidemiology data: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry (NDB)	Routine risk minimization by means of labelling • SmPC Section 4.3. Contraindications • SmPC Section 4.4. Special warnings and precautions for use/ Infections • SmPC Section 4.8. Undesirable effects • Patient Information Leaflet, Sections 2 and 4. Additional risk minimization: • Educational programme • Patient Alert Card
Complications of diverticulitis	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board Epidemiology data: • US claims database • EU registries (BSRBR, ARTIS, RABBIT) • US registry (NDB)	Routine risk minimization by means of labelling: • SmPC Section 4.4. Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • Patient Information Leaflet, Sections 2 and 4. Additional risk minimization: • Educational programme • Patient Alert Card
Serious hypersensitivity reactions	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board Epidemiology data: • US claims database • EU registries (BSRBR, ARTIS, RABBIT) • US registry (NDB)	Routine risk minimization by means of labelling: • SmPC Section 4.4. Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • Patient Information Leaflet, Sections 2 and 4. Additional risk minimization: • Educational programme
Potential risks		
Neutropenia	• Study to address mechanism of neutrophil reduction	Routine risk minimization by means of labelling: • SmPC section 4.2. Posology and

	• Routine pharmacovigilance • Guided Questionnaire for events of special interest will collect neutrophil data in cases of serious infection • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board	method of administration • SmPC section 4.4. Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects/Laboratory evaluations • Patient Information Leaflet, Section 4. • See also Serious Infections above
Thrombocytopenia	• Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: • SmPC section 4.2. Posology and method of administration • SmPC section 4.4. Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects/Laboratory evaluations
Elevated hepatic transaminases	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) to collect information on serious hepatic events • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Nature and frequency of hepatic events representing potential clinical manifestations of increased transaminase levels will be monitored in the registry studies: o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry (NDB)	Routine risk minimization by means of labelling: • SmPC section 4.2. Posology and method of administration • SmPC section 4.4. Special warnings and precautions for use • SmPC section 4.8. Undesirable effects/Laboratory evaluations • Patient Information Leaflet, Sections 2 and 4.
Immunogenicity	• Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: SmPC section 4.8. Undesirable effects/Immunogenicity
Elevated lipids	• Study WA19923 evaluating the effects of IL-6 receptor blockade with tocilizumab (TCZ) on lipids, arterial stiffness, and markers of atherogenic risk in patients with moderate to severe active RA	Routine risk minimization by means of labelling: • SmPC section 4.2. Posology and method of administration • SmPC section 4.4. Special warnings and precautions for use • SmPC section 4.8. Undesirable effects/Laboratory evaluations

	• Routine pharmacovigilance • Ongoing clinical trial programme • Guided Questionnaires on myocardial infarction/acute coronary syndrome, stroke. • Regular review by Roche Pharmacoepidemiology Board • Rate of clinical events potentially related to atherogenesis (e.g. angina, myocardial infarction, cerebrovascular accident) as a potential clinical manifestation of increased lipid levels will be monitored in the registry studies. The nature and rate of such events will be monitored and evaluated on the basis of reports to the: o Sponsor's pharmacovigilance database o US claims database o EU registries (BSRBR, ARTIS, RABBIT) o US registry (NDB)	• Patient Information Leaflet, Sections 2 and 4.
Malignancies	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board Epidemiology data: • US claims database • EU registries (BSRBR, ARTIS, RABBIT) • US registry (NDB)	Routine risk minimization by means of labelling: • SmPC section 4.4. Special warnings and precautions for use • SmPC section 4.8. Undesirable effects

Demyelinating disorders	• Routine pharmacovigilance • Guided Questionnaire (post-marketing data) • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board Epidemiology data: • US claims database • EU registries (BSRBR, ARTIS, RABBIT) • US registry (NDB)	Routine risk minimization by means of labelling: • SmPC section 4.4. Special warnings and precautions for use
CYP450 enzyme normalization	• Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: • SmPC section 4.5. Interaction with other medicinal products and other forms of interaction
Missing information		
Elderly patients	• Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board Epidemiology data: • US claims database • EU registries (BSRBR, ARTIS, RABBIT) • US registry (NDB)	Routine risk minimization by means of labelling • SmPC section 4.2. Special populations/ Elderly Patients
Paediatric patients	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board • Off-label use managed under compassionate use programme Additional studies on efficacy and safety in paediatric patients: • Study WA18221 (SJIA) • Study WA19977(PJIA)	Routine risk minimization by means of labelling: • SmPC Section 4.2. Special Populations/ Paediatric Patients • Patient Information Leaflet, Section 2.
Effects during pregnancy	• Routine pharmacovigilance • Ongoing clinical trial programme • Regular review by Roche Pharmacoepidemiology Board • Registry studies with OTIS • Queries to ENTIS • Pregnancy data from BSRBR and RABBIT	Routine risk minimization by means of labelling: • SmPC section 4.6. Pregnancy and lactation/Pregnancy • Patient Information Leaflet, Section 2.

Hepatic impairment	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling: • SmPC section 4.2. Special populations/Hepatic Impairment • SmPC section 5.2. Pharmacokinetic properties/ Pharmacokinetics in Special Populations • Patient Information Leaflet, Section 2.
Renal impairment	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board	Routine risk minimization by means of labelling • SmPC section 4.2. Special populations/Renal Impairment • SmPC section 5.2. Pharmacokinetic properties/ Pharmacokinetics in Special Populations/Renal Impairment • Patient Information Leaflet, Section 2.
Combination with biologics	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board Epidemiology data: • US claims database • EU registries (BSRBR, ARTIS, RABBIT) • US registry (NDB)	Routine risk minimization by means of labelling: • SmPC section 4.4. Special warnings and precautions for use • Patient Information Leaflet, Section 2.
Vaccinations	• Routine pharmacovigilance • Regular review by Roche Pharmacoepidemiology Board • Substudy to be performed	Routine risk minimization by means of labelling: • SmPC section 4.4. Special warnings and precautions for use /Vaccinations • Patient Information Leaflet, Section 2.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the drug substance are adequately described, controlled and validated. The drug substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the drug product has been satisfactorily described and validated. The quality of the drug product is controlled by adequate test methods and specifications. The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured. Except for a number of quality points, which will be addressed as part of post-approval follow-up measures, the overall Quality of RoActemra is considered acceptable.

Non-clinical pharmacology and toxicology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose. The potential risk for humans is unknown. Adequate labelling is provided in section 4.6 and 5.3 of SPC.

Efficacy

Efficacy has been shown in patients with moderate to severe RA that have an inadequate response to one or more DMARDs including MTX, as well as patients that have an inadequate response or are intolerant to anti-TNF medications. However, although superiority to MTX has been shown in patients that were off MTX at the time of inclusion in the study the supplied data are not considered sufficient to justify a "first line" indication. This is related to the fact that MTX first line therapy is generally considered effective for the treatment of signs and symptoms as well as inhibition of progression of structural damage, while there are no data for tocilizumab showing inhibition of progression of structural damage in a "first line" setting.

For the justification of a "second line" indication after failure of DMARD and/or anti-TNF the applicant has provided a meta-analysis of efficacy and safety that compares anti-TNF medications to tocilizumab in patients that had failed on conventional DMARD. This analysis shows that ACR20 appears to be comparable, and ACR50 and ACR70 appear to be more likely with tocilizumab than anti-TNF medications when using a 24 week endpoint. This data is considered supportive for the "second line" indication.

Evaluation of the inhibition of progression of structural damage was a pre-defined endpoint in study WA17823. The two co-primary 12 month endpoints included prevention of progression of joint damage and improvement in physical function of TCZ therapy in combination with MTX versus MTX alone (with confirmation at 24 months). The study met its two primary endpoints at week 52.

The doses of 4 mg/kg and 8 mg/kg were tested in the majority of studies and both show comparable efficacy. However, patients dosed with 8 mg/kg had consistently higher response rates in the pivotal trials. These clinical efficacy data are supported by pharmacodynamic investigations relating to changes in CRP and haemoglobin giving further evidence for choosing the 8 mg/kg dose. From the performed population PK no dose adjustments appear necessary for age, gender, race or renal impairment. As no hepatic metabolism was noted no impact of hepatic impairment on PK is anticipated, although not formally studied.

The design of the studies and the statistical analysis are considered adequate to determine safety and efficacy in a population with moderate to severe RA. Inclusion and exclusion criteria of the pivotal studies, the design of the studies as well as the obtained baseline characteristics are considered adequate to obtain external validity.

Safety

The main risks with tocilizumab therapy are infections, GI disorders, infusion reactions, skin disorders, neutropenia, elevation in hepatic enzymes and lipid parameters. Certain AE cannot be reliably evaluated due to the relative scarcity of data, this relates to e.g. cardiovascular disorders and malignancies.

Serious infections were more common under the study drug (placebo: 1.5% vs TCZ 2.1%). Within the category of infections, respiratory infections, skin infections and GI were predominant. Systemic infections were rare (3 events of sepsis) and only isolated cases of opportunistic infections were observed. A higher infection rate was observed in patients that had previously received anti-TNF medication.

Gastric disorders (mainly gastritis and upper GI ulcers) were observed more frequently with TCZ combination treatment compared with the control. In 5 cases, the increased inflammation led to perforations and in 2 cases to death. The rate of total GI perforations is 0.184 /100 pt-years which is slightly higher than that reported in the literature for RA patients.

Infusion reactions occurred mainly during the first or second infusion. In the monotherapy groups, 6% in the TCZ 8 mg/kg group and 2% in the MTX group had infusion reactions. In the combination therapy groups ~5% in the TCZ groups and 3% in the placebo groups had infusion reactions. In the long term safety population, these defined events were reported by 6.5% of patients. Infusion reactions comprised mostly hypertension, rash and pruritus. Overall, 12 patients experienced medically significant hypersensitivity reactions (six anaphylactic reactions). Although angioedema was seen more frequently TCZ population 0.87%) than in the placebo groups (0.25%) this was not statistically significant, but warrants further focused investigation in the patients' registries post-authorisation.

Malignancies are increased in patients with RA and additionally with some treatments commonly used in RA (MTX and DMARDs). In the overall clinical trials (including long-term data) the rate of malignancies is 1.27/100 pt-y, it is currently unclear whether this could present an increase and the SPC has been worded accordingly. The 4/5 thyroid neoplasms were shown to be benign in character (one patient was lost to follow-up).

Premature cardiovascular disease is a feature of extra-articular RA, leading to an increased risk for myocardial infarctions, heart failure and cerebrovascular disease. In the studies vascular disorders (mainly hypertension) occurred with up to double the frequency in the TCZ group vs the control groups. In addition, lipid parameters are increased in all TCZ groups, in some studies there is also an increase in atherogenic indices. Viewed long-term the RA population may thus be at an increased risk for ischemic events (in addition to the underlying risk). As the 6 month data is relatively short, it is momentarily difficult to come to a clear conclusion with regard to ischemic events or the possibility of TCZ triggering such events.

Decreases in neutrophil counts were recorded more frequently in the TCZ groups mainly with shifts in CTC grade from normal to -1. These were observed after the first dose of treatment and were sustained throughout the dosing interval. There was little to no clear temporal association between low neutrophil counts and the occurrence of infections. Severe decreases in neutrophil count to < 0.5 x 109/L were infrequent (8 patients in the combination therapy studies and 4 patients in the long-term safety analysis) and led to discontinuation of TCZ after which the neutrophil counts returned to pre-treatment values. Neutropenia as an AE was not reported in the placebo or MTX groups, but in up to 1.4% in the TCZ groups. There also seems to be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

To date the potential for central demyelination with TCZ is unknown. Initially 2 cases were described as optic neuritis and chronic brain ischemia most likely secondary to polycythemia. After completion of the original filing dossier, there was one report of drug-induced leukoencephalopathy (possibly drug-related), one cranial neuropathy, one abnormal nuclear magnetic resonance imaging and one peripheral demyelination.

In the studies elevations in liver function tests were more frequent in the TCZ groups compared to placebo groups but slightly less frequent in the monotherapy compared to MTX. In general these elevations were managed by simple or no intervention. ALT + AST elevations were not associated with simultaneous elevations of bilirubin.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The user testing report should be further developed to be in line with the stated FUM.

Risk-benefit assessment

Benefits:
The pivotal clinical studies have demonstrated a relevant benefit for patients with moderate to severe active RA that have failed on MTX or other DMARDs or anti-TNF drugs. Although two doses were tested in the clinical trials the higher dose of 8 mg/kg shows consistently better efficacy. This benefit is demonstrated by ACR20, ACR50 and ACR70 responses that are clinically relevant, reproducible and show consistent effects across all clinical studies. Consistent results were also demonstrated for the secondary endpoints, e.g. individual ACR components, DAS28 and patient reported outcomes. The design, the quality of conduct and the analysis of the clinical studies are considered sufficient to demonstrate this benefit.

The benefit has been demonstrated on the basis of randomised, double-blinded, controlled 24-weeks trials, maintenance of effect was demonstrated by open label extension trials that allow conclusions for up to one year. Although superior results to MTX have also been shown in a clinical trial including patients that were off MTX therapy at baseline and had shorter disease duration, a situation resembling a first line setting, the current efficacy results are not considered sufficient to grant a marketing authorisation in this population.

The applicant has provided evidence derived from a meta-analysis of efficacy [and safety] comparing anti-TNF medications to tocilizumab. Although the strength of evidence derived from this meta-analysis is considered inferior to results of a clinical trial, the conclusion that tocilizumab and anti-TNF medications appear to have comparable efficacy is acknowledged.

One year radiological data of joint destruction from a dedicated phase III study confirm earlier results in the Japanese population, namely that tocilizumab is effective at inhibiting the progression of structural damage. Unfortunately a direct comparison of effects to other second line therapies is not possible at present because of different scoring systems used.

Tocilizumab has been administered in combination with MTX in the pivotal studies except WA17824 thus the preferable therapy is combination therapy.

Risks:
As identified risks for patients treated with TCZ, Roche reported serious infections, serious hypersensitivity reactions and GI perforation as complication of diverticulitis. Potential risks for further evaluation were neutropenia, thrombocytopenia, liver enzyme elevation and their implications, elevated lipid levels and their implication, especially with regard to cardiovascular and cerebrovascular events, and immunogenicity. For all identified and potential risks, risk minimisation activities have been described. Further to the identified and potential risk, risk identified for other biological DMARDs such as malignancies, demyelinating disorders have been addressed in the RMP. Regarding the effect of TCZ on IL-6 and the known suppression of CYP450 by IL-6, an influence on concentration of drugs metabolized by CYP450 is anticipated.

Missing information for relevant populations as elderly, paediatric patients, pregnant women, patients with impaired hepatic and also renal function as well as the combination with other biologics and vaccination have been addressed, including the description of planned risk minimisation activities.
Beside the reported missing information of the combination with other biological DMARDs there seems to be a tendency of increased frequency of severe neutropenia, when 7 of 8 cases of severe neutropenia occurred in patients with previous treatment with anti-TNF drugs, but only a limited number of patients treated with TCZ received previous anti-TNF treatment. Therefore concomitant treatment with other biological DMARDs is not recommended and a corresponding warning statement has been included in the SPC. Additionally recommendations for monitoring blood cell count during treatment and also recommendations regarding further treatment with tocilizumab when neutrophil count will decrease had been included in the SPC.

Regarding the occurrence of anti-TCZ antibodies and the limitation of the assay, which only measures not bound antibodies, further investigations are necessary. Because of the limitation of the assay there will be an underestimation of the incidence of patients experiencing anti-TCZ antibodies. Especially those patients who experience hypersensitivity reactions or infusion reactions should be tested for anti-TCZ antibodies. The risk for developing anti-TCZ antibodies at re-administration, when TCZ treatment had been interrupted should be investigated. For further evaluation of anti-TCZ antibodies in relation to hypersensitivity reactions and infusion reactions the Applicant had included corresponding questions in the guided questionnaire (see Pharmacovigilance).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Balance:
The overall benefit-risk ratio for Roactemra is considered positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- the following additional risk minimisation activities were required: see as detailed in section 2.3

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of RoActemra in the following indication:

RoActemra, in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate

was favourable and therefore recommended the granting of the marketing authorisation.