Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for tocilizumab (rch)

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

Date of CER:
First round: 21 February 2014
Second round: 28 May 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	20% improvement in JIA ACR score
ACR50	50% improvement in JIA ACR score
ACR70	70% improvement in JIA ACR score
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area Under the Curve (drug concentration-time curve)
AUC_{0-t}	Area under the curve from time 0 to trough
AUC_{inf}	Area under the curve from time 0 to infinity
AUC_{last}	Area under the curve from time 0 to last observation
BMI	Body mass index
CCS	corticosteroids
CDS	Core Data Sheet
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicine Information
Cmax	Maximum concentration
CrCL	Creatinine clearance
CRF	Case Report Form

Abbreviation	Meaning
CRP	C-reactive protein
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CYP450	Cytochrome P450
DAE	Discontinuation due to an adverse event
DAS28	Disease Activity Score 28
DBP	Diastolic Blood Pressure
DMARD	Disease Modifying Anti-Rheumatic Drug
EBV	Epstein-Barr virus
EMA	The European Agency for the Evaluation of Medicinal Products
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	Gastrointestinal
HAQ	Health Assessment Questionnaire
Hb	Haemoglobin
HBV	Hepatitis B virus
HDL	High-density lipoprotein
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
ILAR	International League of Associations for Rheumatology
IM	Intramuscular
IV	Intravenous
ka	absorption rate constant
LDL	Low-density lipoprotein

Abbreviation	Meaning
LFT	Liver function test
LOCF	Last observation carried forward
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MAS	Macrophage Activation Syndrome
MI	Myocardial infarction
mIL-6R	Membrane-bound interleukin-6 receptor
MTX	Methotrexate
NOAEL	No-observed-adverse-effect-level
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OI	Opportunistic infection
PD	Pharmacodynamics
PFS	Pre-filled syringe
PI	Product Information
PIP	Paediatric Investigation Plan
pJIA	Polyarticular juvenile idiopathic arthritis
PJP	Pneumocystis jiroveci pneumonia
PK	Pharmacokinetics
PMS	Post-Marketing Surveillance
PP	Per protocol
PPD	Purified Protein Derivative
PPI	Proton pump inhibitors
PSUR	Periodic Safety Update Report
PY	Patient-years

Abbreviation	Meaning
QoL	Quality of Life
RA	Rheumatoid arthritis
RO4877533	Tocilizumab
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SC	Subcutaneous
sIL-6R	Soluble interleukin-6 receptor
SJC	Swollen joint count
sJIA	Systemic onset juvenile idiopathic arthritis
SPC	Summary of Product Characteristics
TB	Tuberculosis
TCZ	Tocilizumab
TEAE	Treatment emergent adverse event
TG	Triglyceride
TJC	Tender joint count
TNF	Tumour necrosis factor
Tmax	Time to maximum plasma concentration
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VASP	Physicians global score of disease activity at baseline

1. Introduction

This is a Category 1 type C submission to register an extension of indication for Actemra (tocilizumab) 20 mg/mL concentrated solution for infusion. The application also provided additional clinical data which was a post-approval commitment of submission PM-2008-0256-3 and data to support an update to the precaution section of the product information.

The approved indication for Actemra is:

> ***Rheumatoid Arthritis***
>
> *ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> > *in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or*
> >
> > *as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*
>
> *ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.*
>
> ***Systemic Juvenile Idiopathic Arthritis***
>
> *ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. ACTEMRA can be given alone or in combination with methotrexate (MTX).*

The proposed indication for Actemra (with changes underlined) is:

> ***Rheumatoid Arthritis***
>
> *ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> > ***in combination with methotrexate (MTX) in those not previously treated with MTX****;*
> >
> > *in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or*
> >
> > *as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*
>
> *ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given* ***alone or*** *in combination with methotrexate.*
>
> ***Systemic Juvenile Idiopathic Arthritis***
>
> *ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. ACTEMRA can be given alone or in combination with methotrexate (MTX).*

2. Clinical rationale

Rheumatoid arthritis is a progressive systemic autoimmune disease characterised by inflammation of the synovium leading to irreversible destruction and disability of the joints. The treatment of rheumatoid arthritis (RA) is directed toward the control of synovitis and the prevention of joint injury. Clinical recommendations which support an early aggressive

approach to treatment are based upon the observations that joint damage, which may ultimately result in disability, begins early in the course of disease and that the longer active disease persists the less likely the patient is to respond to therapy.

Current therapy consists of anti-inflammatory therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, to help control symptoms and the disease modifying antirheumatic drugs (DMARDs). In patients with moderately to severely active RA (as defined by at least 5 inflamed joints, elevated acute phase reactants and sometimes early radiographic changes) treatment with a DMARD is recommended. These drugs include methotrexate (MTX) and biologic agents. Most biologic agents for treatment of early RA are TNF antagonists. The Sponsor states that there is a clinical need for alternative biological agents with different mechanisms of action which can be used in the early RA population. In addition, while MTX is the main DMARD used, some patients may have intolerance or have comorbidities which contraindicate its use. For these reasons tocilizumab was assessed in combination with MTX and as monotherapy in an early RA population.

Tocilizumab (TCZ; Actemra, RoActemra) is a recombinant, humanised antihuman interleukin (IL)-6 receptor monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors, thereby inhibiting IL-6-mediated signalling. IL-6 is a pro-inflammatory, multifunctional cytokine produced by a variety of cell types. Elevated IL-6 levels have been reported in the serum and synovial fluid of patients with rheumatoid arthritis (RA), and IL-6 levels are reported to correlate with disease activity.

2.1. Guidance

The following information was provided by the sponsors at the pre-submission stage:

As part of this application the Sponsor proposes to revise the existing progression of joint damage claim, as follows: *"ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given alone or in combination with methotrexate."* To support this revision the application includes radiographic data for up to one year of treatment from the WA19926 study. When the study is complete at Week 104, two-year radiographic data will also be available. Radiographic data from the previously submitted MRA012JP and the WA17823 studies are also referred to.

The Sponsor acknowledges the TGA currently adopts the EMA guideline CPMP/EWP/556/95 Rev 1 Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis, dated December 2003, which includes the following requirement for radiographic data: "For agents which are claimed to prevent structural joint damage, it is currently recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons taken not less than one year apart ideally for two years using full randomisation and pre-agreed criteria."

However the new draft EMA guideline CPMP/EWP/556/95 Rev 2 Guideline on clinical investigation of medicinal products other than NSAIDs for the treatment of rheumatoid arthritis, dated 28 November 2011, has updated this requirement as follows:

"Using the existing validated technique to assess radiographic progression, i.e. radiographs, measurement after 1 year may be sufficient to confirm efficacy in terms of endpoints relevant to slowing/prevention of structural damage claim. In exceptional cases a measurement after at least 6 months may be sufficient depending on the properties of the test drug; this has to be justified by robustness of the method and convincing clinical data. It is important to demonstrate long-term maintenance of this effect for an additional 12 months".

The Sponsor considers sufficient data are provided in this application to address these requirements.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5:

- One population PK study (WA17823).
- One phase III study (WA19926).
- One phase III extension study (WA18695).
- One phase IV study (NA25256).
- Literature references.

Module 1

- Application letter, application form, proposed amended Australian PI and CMI, EU Risk Management Plan and Australian Specific Annex

Module 2

- Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety, individual study synopses and listing of literature references.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

The studies included in the dossier all included statements that they were conducted in accordance with ICH Good Clinical Practice guidelines as well as local ethical and regulatory requirements.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The dossier included a population PK study report 103077 which was based on samples collected in study WA17823.

4.2. Summary of pharmacokinetics

The following information in relation to RA and sJIA is from the approved product information.

Rheumatoid arthritis

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1793 RA patients treated with a one hour infusion of 4 and 8 mg/kg every 4 weeks for 24 weeks.

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

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

The following parameters are valid for a dose of 8 mg/kg tocilizumab given every 4 weeks. Predicted mean (±SD) steady-state AUC, Cmin and Cmax of tocilizumab were 35000 ± 15500 h·µg/mL, 9.74 ± 10.5 µg/mL, and 183 ± 85.6 µg/mL, respectively. The accumulation ratios for AUC and Cmax were small; 1.22 and 1.06, respectively. The accumulation ratio was higher for Cmin (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for Cmax, AUC, and Cmin, respectively. Tocilizumab AUC, Cmin and Cmax increased with increase of body weight. At body weight ≥≥100 kg, the predicted mean (± SD) steady-state AUC, Cmin and Cmax of tocilizumab were 55500 ± 14100 h·µg/mL, 19.0 ± 12.0 µg/mL, and 269 ± 57 µg/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see *DOSAGE AND ADMINISTRATION*).

The following parameters are valid for a dose of 4 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, Cmin and Cmax of tocilizumab were 13000 ± 5800.µg.h/mL, 1.49 ± 2.13 µg/mL, and 88.3 ± 41.4 µg/mL, respectively. The accumulation ratios for AUC and Cmax were small; 1.11 and 1.02, respectively. The accumulation ratio was higher for Cmin (1.96). Steady-state was reached following the first administration for both Cmax and AUC and from 16 weeks for Cmin.

Systemic juvenile idiopathic arthritis

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with systemic juvenile idiopathic arthritis (sJIA) treated with 8 mg/kg (patients with a body weight ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg), given every 2 weeks. The predicted mean (±SD) AUC_{2weeks}, Cmax and Cmin of tocilizumab were 32200 ± 9960 µg.hr/mL, 245 ± 57.2 µg/mL and 57.5 ± 23.3 µg/mL, respectively. The accumulation ratio for Cmin (week12/week2) was 3.2 ± 1.3. The tocilizumab Cmin was stabilised after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

Distribution

Following IV dosing, tocilizumab undergoes biphasic elimination from the circulation. In RA patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

In paediatric patients with sJIA, the central volume of distribution was 0.94 L and the peripheral volume of distribution was 1.60 L resulting in a volume of distribution at steady state of 2.54 L.

Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in RA patients and 7.1 mL/h in paediatric patients with sJIA. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

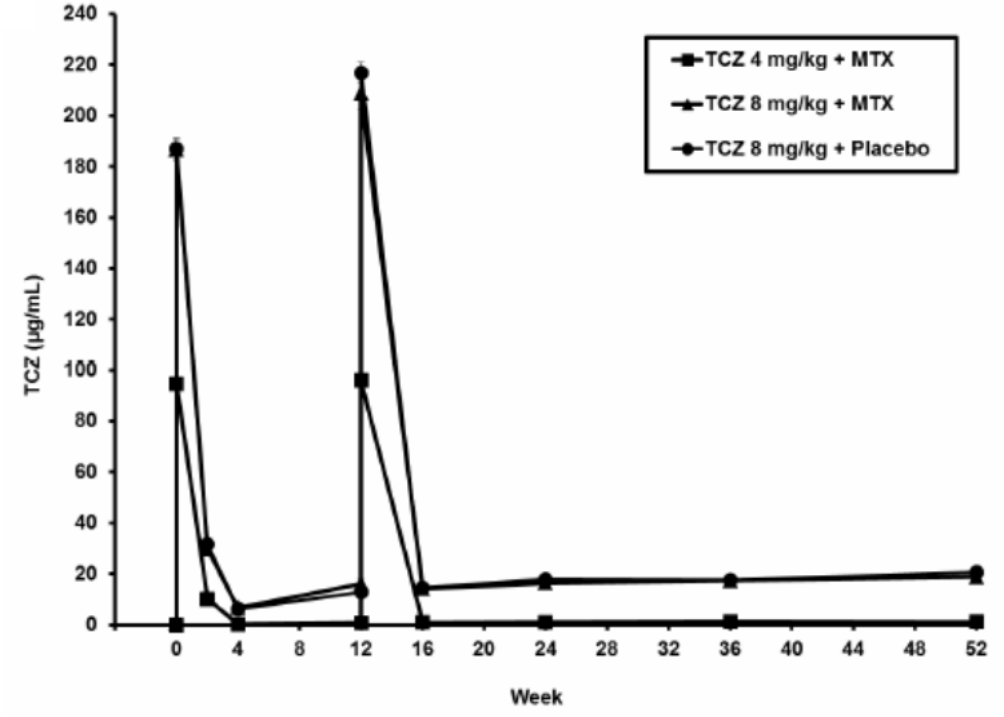
The half life (t½) of tocilizumab is concentration-dependent in RA, the concentration-dependent apparent t½ is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. The t½ of tocilizumab in children with sJIA is up to 23 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

4.2.1. Pharmacokinetics in the target population

WA17823 was a randomised, double-blind, and parallel group study of the safety and prevention of structural joint damage during treatment with tocilizumab versus placebo, in combination with methotrexate (MTX), in patients with moderate to severe active rheumatoid arthritis. The dossier included the population PK report number 1031077 which analysed data (3336 samples from 841 patients) from this 52 week study. The original population PK model, a two-compartment disposition model with parallel first-order and Michaelis-Menten elimination kinetics, was based on data from four phase III studies of 24 months duration. This original PK model was found to adequately describe the longer treatment duration data from study WA17823.

WA19926 was a phase III, randomised, double-blind, parallel group study of treatment with tocilizumab versus placebo, in combination with methotrexate (MTX), in patients with early, moderate to severe active rheumatoid arthritis (see Section 7.1.1.1). Data were provided to week 52 of treatment. PK analysis found that the mean TCZ pre-dose concentrations levelled from week 16 across the treatment groups (Figure 1).

Figure 1: Mean (SEM) TCZ concentrations (µg/mL)



Note: SEMs are not visible for all visits / treatment groups

Steady-state Cmin TCZ concentrations in the 4 and 8 mg/kg TCZ dose levels were approximately 1 and 17–21 µg/mL, respectively. Cmax at week 12 were approximately 96 and 209–217 µg/mL at 4 mg/kg and 8 mg/kg TCZ dose levels, respectively. The TCZ PK were comparable between both groups treated with 8 mg/kg TCZ with or without concomitant MTX.

Scatter plots showed no correlation between DAS28 scores at week 24, or mTSS scores at Week 52, and corresponding Cmin values. There was a trend for increasing proportion of DAS28 responders with increasing quartile of Cmin from Q1 to Q3 but this did not continue for Q4.

4.3. Evaluator's overall conclusions on pharmacokinetics

The PK data from the 52 week study WA17823 were adequately described by the reference PK model generated using data from four phase III 24 week studies.

Pharmacokinetics in the early severe RA population were consistent with that observed in RA patients with inadequate response to anti-TNF or other DMARDs.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The population PK study report 103077 contained data on radiographic findings and tocilizumab exposure from patients in study WA17823.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from the approved product information.

5.2.1. Mechanism of action

Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Tocilizumab binds specifically to both soluble and membrane-bound IL 6 receptors, and has been shown to inhibit sIL 6R and mIL 6R-mediated signaling. IL-6 is a multi-functional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of inflammatory diseases, including rheumatoid arthritis (RA).

The possibility exists for tocilizumab to affect host defences against infections and malignancies. The role of IL-6 receptor inhibition in the development of malignancies is not known.

5.2.2. Pharmacodynamic effects

In clinical studies with tocilizumab, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed. Rapid increases in haemoglobin levels (within the first 2 weeks) were also observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts (ANC) decreased to their lowest levels 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Patients with RA demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration.

5.2.3. Relationship between drug concentration and pharmacodynamic effects

A secondary objective of the population PK study 103077 was to evaluate the relationship between TCZ exposure and radiographic findings in the subset of patients from study WA18723. TCZ exposure over the 52 week study was categorised into high, medium and low. Radiographic assessments included erosion score, joint space narrowing score and modified Sharp score (combination of erosion and joint space narrowing). A graphical analysis was undertaken for these variables and showed that there may be an improvement in these variables with higher TCZ exposure.

> **Comment**: The graphical nature of the data mean that it is not possible to draw definitive conclusions.

5.3. Evaluator's overall conclusions on pharmacodynamics

The radiograph data from study WA17823 were presented graphically against categorised tocilizumab exposure and were suggestive of a possible improvement in modified Sharp score with higher TCZ exposure.

6. Dosage selection for the pivotal studies

There were no proposed alterations to the current approved dosage regimen of 8 mg/kg given once every 4 weeks as an IV infusion. The maximum dose is 800 mg per infusion. The submitted trial WA19926 had treatment arms of tocilizumab 4 mg/kg and 8 mg/kg given by IV infusion every 4 weeks. The primary efficacy analysis was of the 8 mg/kg dose.

7. Clinical efficacy

7.1. Treatment of early RA, MTX-naïve patients

7.1.1. Pivotal efficacy studies

7.1.1.1. Study WA19926

7.1.1.1.1. Study design, objectives, locations and dates

WA19926 was phase III randomised, double-blind, parallel group study of safety, disease remission and prevention of structural joint damage during treatment with tocilizumab (TCZ), as a monotherapy and in combination with methotrexate (MTX), versus methotrexate in patients with early, moderate to severe rheumatoid arthritis. It was conducted between September 2009 and May 2012 at 237 centres in 35 countries. The study was also known as Function.

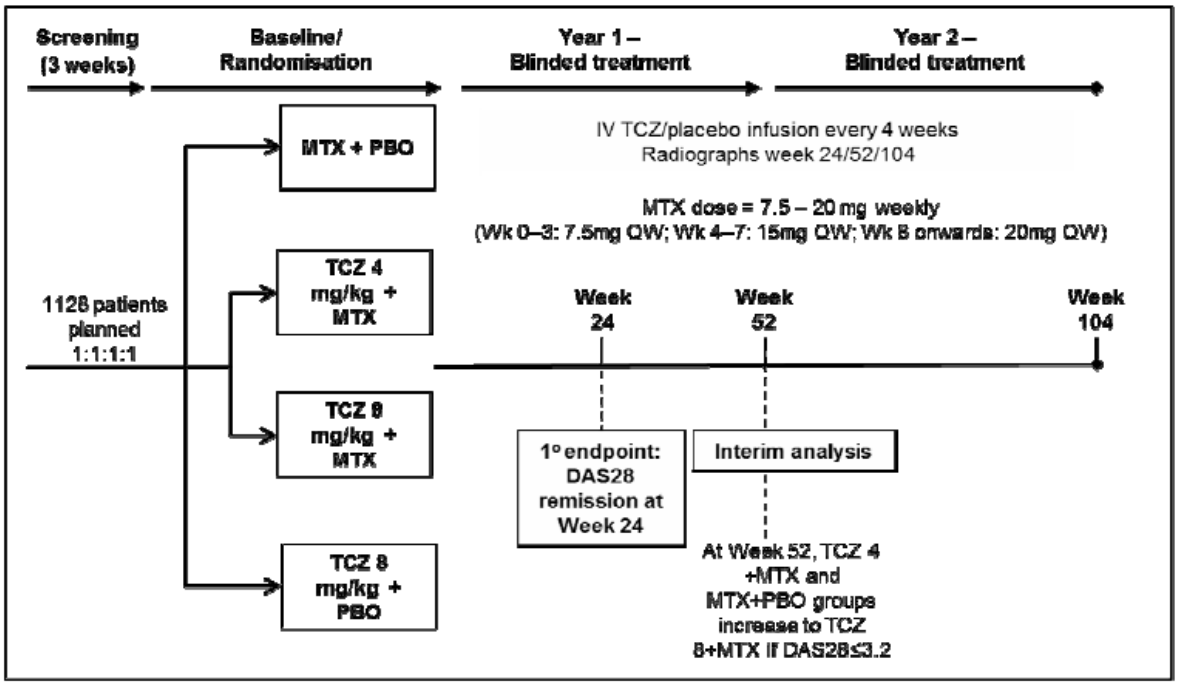
The primary objective was to assess the efficacy of 6 months treatment with TCZ in combination with MTX and TCZ monotherapy versus MTX monotherapy in patients with early, moderate-to severe RA.

The secondary objectives were:

- Prevention of structural joint damage over 12 months and maintenance of this effect at 24 months;
- Improvement in physical function over 12 months and maintenance of this effect at 24 months;
- Pharmacokinetics, immunogenicity, and pharmacodynamics of TCZ in patients with early RA; and
- Safety of TCZ administration in patients with early RA.

After a 21 day screening period, eligible subjects were randomised to one of 4 treatment groups. The primary efficacy analysis was conducted at week 24 (6 months) and blinded treatment continued to week 104 (2 years) (Figure 2). Data were provided to 52 weeks in the submitted CSR.

Figure 2: Study WA19926 design



Efficacy parameters were assessed at baseline, weeks 2 and 4, then every 4 weeks up to week 24, and then at weeks 28, 36, and 52. Radiographs of the hands, wrists, and feet of each patient were obtained at screening, weeks 24 and 52. For efficacy and safety assessments, a "dual assessor" approach was used to prevent potential unblinding. A separate "joint assessor" (who was not the principal investigator) completed the joint counts while the treating physician completed the other assessments. There was a central laboratory for Xray analysis which was conducted by blinded readers.

7.1.1.1.2. Inclusion and exclusion criteria

Patients enrolled were adult (≥18 years) men or women with moderate to severe active early RA of ≤ 2 years' disease duration. RA was diagnosed according to the 1987 revised American College of Rheumatology (ACR) criteria. Other inclusion criteria were:

- DAS28 >3.2 both at screening and baseline visits
- Swollen joint count (SJC) ≥4 (66 joint count) and tender joint count (TJC) ≥6 (68 joint count) at screening and baseline visits.
- Erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr or C-reactive protein (CRP) ≥10 mg/L at screening visit.
- Positivity for either rheumatoid factor or anti-CCP antibodies (Abs) at screening or if negative for rheumatoid factor and anti-CCP Ab, ≥1 erosion of hands, wrists, or feet at screening (erosion determined by central reading of X-rays).
- No previous treatment with MTX or a biologic agent.
- Oral corticosteroids (≤10 mg/d oral prednisolone or equivalent) if the dose was stable for at least 4 weeks.
- NSAIDS if the dose was stable for at least 2 weeks.
- Negative serum pregnancy test.

Exclusion criteria were:

- Major surgery (including joint surgery) within 8 weeks or planned major surgery within 6 months.
- Rheumatic autoimmune disease other than RA including SLE, mixed connective tissue disease (MCTD), scleroderma, and polymyositis, or significant systemic involvement secondary to RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome). Secondary Sjögren's syndrome and/or nodulosis with RA was permitted.
- Functional class IV as defined by the ACR Classification of Functional Status in RA.
- History of or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease).
- Treatment with MTX or a biologic agent (including TCZ) at any time prior to baseline.
- Treatment with any investigational agent within 4 weeks.
- Previous treatment with any cell depleting therapies, including investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20)
- Treatment with IV gamma globulin, plasmapheresis, or Prosorba column within 6 months.
- Intra-articular (IA) or parenteral corticosteroids within 6 weeks prior to screening visit.
- Immunisation with a live/attenuated vaccine within 4 weeks prior to baseline visit.
- Any previous treatment with alkylating agents, such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.
- History of severe allergic or anaphylactic reactions to monoclonal antibodies.
- Current or previous (within the past 2 years) evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), or gastrointestinal (GI) disease.
- Uncontrolled disease states, such as asthma or inflammatory bowel disease for which flares are commonly treated with oral or parenteral corticosteroids.
- History of diverticulitis, diverticulosis requiring antibiotic treatment, or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations.
- Current liver disease.
- Active infection or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, including, but not limited to, tuberculosis (TB) and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds.
- Any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening visit.
- Active TB requiring treatment within the previous 3 years. Patients had to be screened for latent TB following local practice guidelines and were not allowed to be admitted to the study if latent TB was detected. Patients had to have no evidence of active TB infection at enrollment. Patients treated for TB with no recurrence within 3 years were permitted.
- Primary or secondary immunodeficiency (history of or currently active)
- Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including hematologic malignancies and solid tumors, except basal cell carcinoma of the skin that has been excised and cured), or breast cancer diagnosed within the previous 20 years.

- Pregnant women or breast feeding mothers.
- History of alcohol, drug or chemical abuse within the 6 months prior to screening.
- Neuropathies or other painful conditions that might interfere with pain evaluation.
- Serum creatinine >1.6 mg/dL (141 µmol/L) in female patients and >1.9 mg/dL (168 µmol/L) in male patients.
- ALT or AST >1.5 ×the upper limit of normal (ULN), total bilirubin >ULN.
- Platelet count <100,000 /mm^3 (100 ×109/L).
- Haemoglobin < 8.0 g/dL (5.0 mmol/L).
- White blood cells <3000/mm^3 (3.0 ×109/L).
- Absolute neutrophil count (ANC) <2000/mm^3 (2.0 ×109/L).
- Absolute lymphocyte count <500/mm^3 (0.5 ×109/L).
- Positive hepatitis B surface antigen or hepatitis C antibody.

7.1.1.1.3. Study treatments

Treatment was with TCZ 4 mg/kg IV, TCZ 8 mg/kg IV or matching IV placebo every four weeks for the duration of the study. Treatment was given on an outpatient basis. The infusion was made up with a 100 mL bag of normal saline with the number of 10 mL vials (20 mg TCZ/mL or placebo) dependent on the patient's body weight. It was given at 10 mL/hour for 15 minutes and then increased to 130 mL/hr with dosing finished by 1 hour. At week 52, subjects in the 4 mg/kg +MTX and the placebo+MTX groups with a DAS28 of ≥3.2 could change to treatment with TCZ 8 mg/kg+MTX.

Oral and IV study drug was withheld if ALT/AST were >1.5x ULN and resumed when ≤1.5x ULN. The patient was withdrawn if 3 consecutive treatments were missed due to liver enzyme elevations or if ALT/AST were >5x ULN or if ALT/AST were >3x ULN with bilirubin >2x ULN. The protocol provided strategies for dose reduction, interruption, or discontinuation for other adverse events of special interest.

Background therapy was with MTX weekly or matching oral placebo. MTX was in a 2.5 mg oral capsule with dosing commencing at 7.5 mg (3 capsules). The dose was increased to 15 mg weekly at week 4 and 20 mg weekly at week 8 if there were any swollen or tender joints. Dose reduction or interruption were allowed for MTX-related side effects. Specific criteria were specified for raised ALT and AST. If the dose was <7.5 mg per week, or 7 consecutive weekly doses were missed for raised LFTs, the patient was withdrawn.

Stable NSAID and oral corticosteroid (≤10 mg/day prednisone equivalent) doses were continued during the study. Intra-articular glucocorticoids were discouraged and IV or IM administration prohibited. Other DMARDs were also prohibited. All patients received folic acid 5 mg (or equivalent) per week.

7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables (see definitions below) were:

- Disease Activity Score 28 (DAS28). The primary efficacy endpoint was the DAS28 remission rate at 24 weeks, with the remission defined as a DAS of <2.6.
- American College of Rheumatology improvement scores ARC20, ARC50, ARC70
- Joint damage using the modified Sharp Score (mTSS)
- Joint erosion score

- Joint space narrowing (JSN) score
- HAQ-DI
- SF-36

Definitions:

– The DAS28, Disease Activity Score 28, is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis. It was calculated as follows (Figure 3):

Figure 3: Calculation formula for Disease Activity Score 28

$$DAS28 = \left(0.56 \times \sqrt{28TJC}\right) + \left(0.28 \times \sqrt{28SJC}\right) + \left(0.7 \times \log_e ESR\right) + \left(0.014 \times GH\right),$$

where 28TJC and 28SJC are the TJCs and SJCs from 28 joints, respectively, GH (global health) is the patient's global assessment of disease activity, and ESR is in mm/hour. If ESR equals zero mm/hour, then the ESR result will be set to 1 mm/hour for the purpose of the DAS28 calculation.

– An ACR20 response required at least a 20% improvement compared with baseline in both 66TJCs and 68SJCs as well as in 3 of 5 of the additional ACR core set variables: physician's global assessment of disease activity VAS, patient's global assessment of disease activity VAS, patient's assessment of pain VAS, HAQ-DI, and an acute phase reactant (CRP or ESR). CRP was used as the acute phase reactant for the calculation of the ACR response, since this was analysed centrally (ESR was analysed locally). However, where the percentage change from baseline for CRP is missing, ESR will be substituted. The ACR50 and ACR70 responses required a 50% and 70% improvement respectively, relative to baseline for the same criteria as described for the ACR20.

– The degree of joint damage was assessed using a modification of the Sharp score (mTSS). The methodology quantifies the extent of bone erosions for 44 joints and joint space narrowing (JSN) for 42 joints, with higher scores representing greater damage. The maximum mTSS is a combination of the Erosion Scoring and the JSN Scoring.

– The joint erosion score is a summary of erosion severity in 32 joints of the hands and 12 joints in the feet. Each joint in the hand is scored from 0 to 5, and each joint in the foot is scored from 0 to 10. The maximum erosion score is 280 for a timepoint. Each joint is scored according to the surface area involved. The highest score (5 for the hand and 10 for the foot joints) indicates extensive loss of bone from more than one-half of the articulating bone. A score of 0 in either the hand or foot joints indicates no erosion.

– The JSN score summarizes the severity of JSN in 30 joints of the hands and 12 joints of the feet. Assessment of JSN for each hand (15 joints per hand) and foot (6 joints per foot), including subluxation, is scored from 0 to 4. The maximum JSN score is 168.

– The Stanford HAQ-DI is a self-completed patient questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The scores range from 0 to 3. A change from baseline of –0.22 is considered to be the minimal clinically important difference (MCID).

– The SF-36 (version 2) is a standardised questionnaire consisting of 36 questions used to assess a patient's health across eight dimensions: general health, mental health, physical functioning, social functioning, vitality, bodily pain, role limitation due to physical function, role limitation due to emotional function.

Secondary endpoints included:

- Proportion of patients with a DAS28 remission response at Week 52.
- Proportion of patients with ACR20 response at Week 24 and Week 52.
- Proportion of patients with ACR50 response at Week 24 and Week 52.
- Proportion of patients with ACR70 response at Week 24 and Week 52.
- Change from baseline in modified Total Sharp score (mTSS) at Week 52.
- Change from baseline in modified Sharp erosion score at Week 52.
- Change from baseline in modified Sharp JSN score at Week 52.
- Major clinical response (defined as achieving a continuous 6-month period of success by the ACR70) at Week 52.
- Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) score at Weeks 24 and 52.
- Change from baseline in Short Form 36 (SF-36) physical component summary (PCS) scores at Weeks 24 and 52.

There were a large number of exploratory endpoints for which there was no controlling of multiplicity in the analysis.

7.1.1.1.5. Randomisation and blinding methods

Subjects were randomised by an IVRS to one of four groups in a 1:1:1:1 ratio. Randomisation was stratified by serologic status (rheumatoid factor and/or anti−cyclic citrullinated peptide [anti-CCP] antibody positivity) and by geographic region.

The study was double blind and double dummy. TCZ or placebo was supplied in matching vials of 10 mL. MTX was blinded by overencapsulation with additional lactose filler. Placebo capsules contained only the lactose filler. Eleven patients were withdrawn from the study and unblinded due to safety concerns and one unblinded for a site transfer.

7.1.1.1.6. Analysis populations

Primary analysis was on the ITT population which consisted of all randomised patients who received at least one TCZ/placebo infusion.

7.1.1.1.7. Sample size

Assuming a DAS28 remission response rate of 26% and 16% in the TCZ 8 mg/kg+MTX and placebo+MTX groups, respectively (using data from studies WA17824 and WA17823), a total of 1128 patients (282 patients per group) were expected to achieve 80% power to detect an absolute difference of 10% between DAS28 remission rates of the TCZ 8 mg/kg + MTX treatment group and the placebo + MTX treatment group in a two-sided test at a 5% significance level.

In addition, the sample of 282 patients per group gave the study a 98% power to detect a mean difference of 2.17 units between the TCZ 8 mg/kg+MTX group and the placebo+MTX group (two-sided test at α=5%) assuming a modified total Sharp score (mTSS) of 0.27 and 2.44 units in the respective groups and 10% of patients did not have the required baseline and one post-baseline radiographic assessment.

7.1.1.1.8. Statistical methods

The primary comparison was between the TCZ 8 mg/kg +MTX and the placebo+MTX groups. Patients withdrawing prior to week 24 or without a week 24 assessment were classified as non-responders. Between group comparison of the primary endpoint (DAS28 remission) was

undertaken using logistic regression with stratification factors (serological status and geographical region) as covariates. Imputation methods included the LOCF for SJCs and TJSs. Supportive analysis was with a Cochran-Mantel-Haenszel chi-square test.

Secondary endpoints were analysed as follows:

- non-parametric analysis of covariance for the comparison of change from baseline in radiographic scores;
- logistic regression for binary response variables, such as the ACR20 response;
- analysis of covariance for continuous variables (other than radiographic scores), such HAQ-DI score

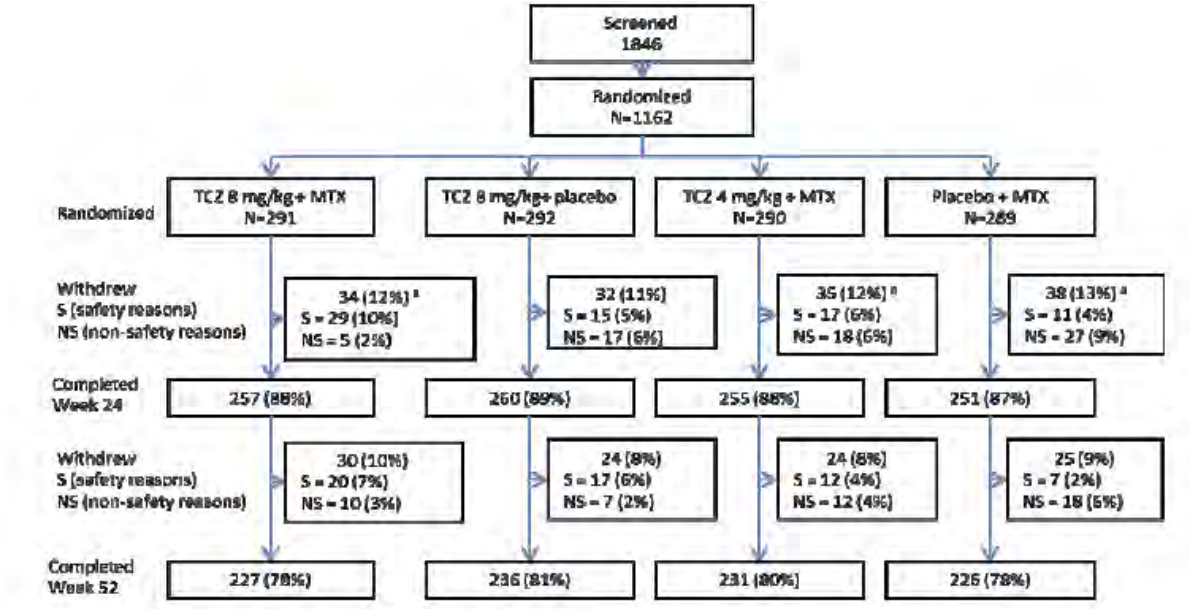
Analysis of secondary endpoints was in a fixed sequential order to control the type I error for multiple comparisons.

PK samples for TCZ concentration were collected pre-dose at baseline and weeks 2, 4, 12, 16, 24, 36, and 52. Analysis of Cwk2 (µg/mL), Cmin (µg/mL) and Cmax (µg/mL) was descriptive.

7.1.1.1.9. Participant flow

There were 1846 patients screened, 1162 randomised and 1157 were treated (289-292 per group) and comprised the ITT population. The rate of week 24 and week 52 completion was 87-89% and 78-81%, respectively (Figure 4).

Figure 4: WA19926 Patient disposition



[a] 5 patients (2 [placebo + MTX], 2 [TCZ 4 mg/kg + MTX], 1 [TCZ 8 mg/kg + MTX]) withdrew from the study due to non-safety reasons, and did not receive any study treatment (and were excluded from analysis populations) (source: page 508).

Percentages are based on number of patients randomized.

Source: page 509 , page 510 , and page 511

The rates of premature withdrawal were similar between groups. To week 24, withdrawals due to safety events were higher in the TCZ 8 mg+ MTX group compared to the other groups (10% vs 4-6%) while non safety reasons (including insufficient response) were higher in the placebo+MTX group (9% vs 2-6%). This trend continued to week 52 with the overall withdrawal rate remaining similar between groups (19-22%).

7.1.1.1.10. Major protocol violations/deviations

There were 16 patients with major protocol violations leading to study withdrawal: 4 in the TCZ 8 mg/kg+MTX; 1 in the TCZ 8 mg/kg+placebo; 5 in the TCZ 4 mg/kg+MTX; and 6 in the

placebo+MTX group. A further 12 patients had inclusion/exclusion violations which did not result in withdrawal. The overall major violation rate was 2.4%.

The protocol was amended twice. The first amendment was the inclusion of a separate protocol for the same study which allowed European sites to be involved without them being included in the US IND application. Study conduct changes included capping dose of TCX at 800 mg for patients weighing >100 kg and removing the upper weigh limit for patients. The second amendment required that patients experiencing anaphylaxis or serious hypersensitivity were to discontinue treatment. This was due to one such fatal post-marketing case.

7.1.1.1.11. Baseline data

Overall, the treatment groups were balanced on demographic and baseline disease characteristics. The patients were largely Caucasian (76-79%), females (75-80%) with a mean age of 49-51 years (range 18-84 years). The mean RA duration was 0.4-0.5 years, 89-91% were positive for RF, 86-87% for anti-CCP antibody and the mean and median DAS28 was 6.6-6.7 and 6.5-6.8, respectively. Prior use of DMARDs was low with 76-82% being DMARD-naïve.

Other baseline disease characteristics (SJC66, TJC68, ESR, CRP, HAQ-DI, Pain VAS, physician VAS and Global VAS score) were relatively balanced across groups.

The most frequent concurrent diseases were hypertension (28-33%) and osteoarthritis (9-12%). Concomitant medication use was frequent (96-97%) with NSAIDs, corticosteroids and analgesics being the most frequent.

7.1.1.1.12. Results for the primary efficacy outcome

The rate of DAS28 remission at week 24 was 15.0%, 31.9%, 44.8% and 38.7% in the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively. The primary comparison of TCZ 8 mg+MTX versus placebo+MTX (44.8% vs 15.0%) was statistically significant ($p<0.0001$) with an odds ratio of 4.8 (95% CI: 3.2, 7.1). The TCZ 8 mg monotherapy group also had a significantly greater response on DAS remission at week 24 compared to MTX (38.7 vs 15.0%, OR=3.7, $p<0.0001$) but while the TCZ 4mg +MTX regimen had a numerically greater result it was not significant in the hierarchical testing. Results of analysis using Cochran-Mantel-Haenszel methods were consistent with logistic regression.

7.1.1.1.13. Results for other efficacy outcomes

The hierarchical process for statistical testing shows that the first 13 endpoints were statistically significant (Table 1) with the remainder (14 to 48, [not shown here]) not reaching statistical significance.

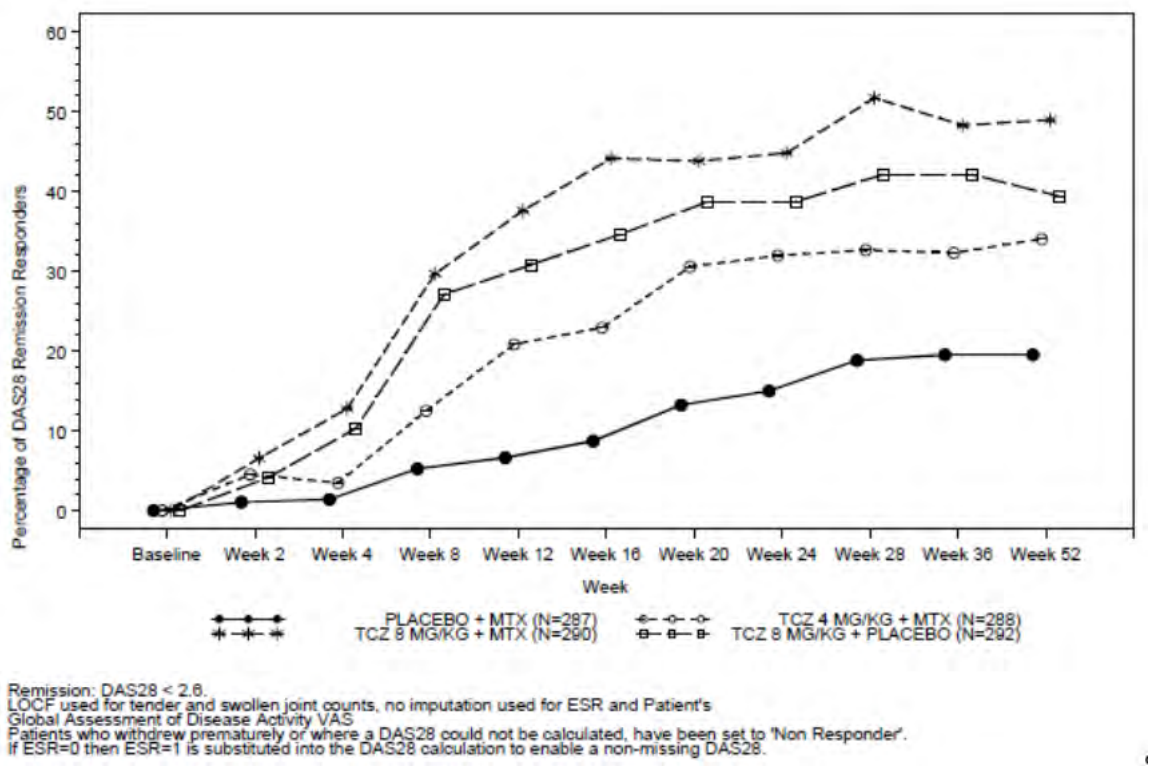
Table 1: Hierarchical chain for statistical testing (endpoints 1-13)

Order	Endpoint	TCZ Dose (mg/kg) Compared with Placebo + MTX	p-value (Hierarchy)
1	Proportion of patients with a DAS28 remission response (DAS28 < 2.6) at Week 24	8 + MTX	<0.0001
2	Proportion of patients with ACR50 response at Week 24	8 + MTX	0.0009
3	Proportion of patients with ACR70 response at Week 24	8 + MTX	0.0006
4	Proportion of patients with ACR20 response at Week 24	8 + MTX	0.0142
5	Change from baseline in modified total Sharp scores (mTSS) at Week 52	8 + MTX	0.0001
6	Change from baseline in modified Sharp erosion score at Week 52	8 + MTX	0.0006
7	Proportion of patients with a DAS28 remission response (DAS28 < 2.6) at Week 52	8 + MTX	<0.0001
8	Proportion of patients with ACR50 response at Week 52	8 + MTX	0.0003
9	Proportion of patients with ACR70 response at Week 52	8 + MTX	0.0003
10	Proportion of patients with ACR20 response at Week 52	8 + MTX	0.0118
11	Change from baseline in HAQ-DI score at Week 52	8 + MTX	0.0024
12	Change from baseline in HAQ-DI score at Week 24	8 + MTX	0.0011
13	Proportion of patients with a DAS28 remission response (DAS28 < 2.6) at Week 24	8 (monotherapy)	<0.0001

Comparisons of the TCZ 8 mg+MTX group to placebo+MTX were significant for the following variables: DAS28 <2.6, ACR20, ACR50, ACR70, HAQ-DI at week 24 and 52 and the mTSS and mSES at week 52. In addition, the comparison between the TCZ 8 mg monotherapy and placebo+ MTX groups also reached significance for DAS28 <2.6 at week 24. Other comparisons of the TCZ 8 mg monotherapy and the TCZ 4 mg+MTX groups to the placebo+MTX group were not significant due to the break in hierarchical testing.

The DAS28 remission response rates at week 52 were 19.5%, 34.0%, 49.0% and 39.4% in the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively. The response rates were significantly greater with TCZ 8 mg+MTX than placebo+MTX with an OR=4.2 (95% CI: 2.9,6.1, p<0.0001). Figure 5 shows a maintenance of effect from week 24 to 52.

Figure 5: Study WA19926. Percentage of patients with DAS28 remission status by visit (ITT population)



Exploratory analysis found that 79.2% of week 24 responders were still responders at week 52 in the TCZ+MTX group compared to 55.8% in the placebo+MTX group.

Exploratory analysis found the adjusted mean change in DAS28 score from baseline to week 24 was significantly greater in all TCZ groups than in the placebo+MTX group.

Analysis of week 24 DAS28 components rates by ANOVA found significant improvements in the adjusted mean differences for SJCs, TJCs, ESR for all TCZ groups compared to placebo+MTX while the difference for patient global assessment VAS was not significant for the TCZ 8 mg+placebo group comparison.

Exploratory analysis of the proportion of patients achieving EULAR response by treatment week is shown in Figure 6 shows consistently greater rates of "good response" (see Table 2 for definition) in the TCZ groups through to week 52.

Figure 6: Study WA19926. Percentage of patients in each EULAR response category by visit (ITT population)

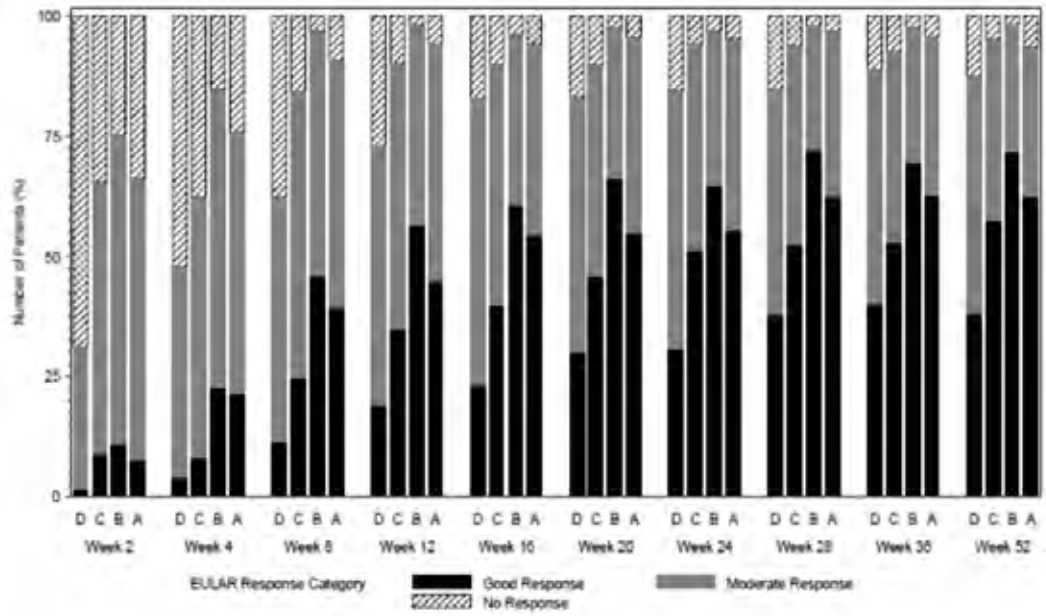


Table 2: EULAR response definition

Score at Visit	Improvement		
	< – 1.2	≥ – 1.2 to < – 0.6	≥ – 0.6
DAS28 ≤ 3.2	Good response	Moderate response	No response
> 3.2 DAS28 ≤ 5.1	Moderate response	Moderate response	No response
DAS28 > 5.1	Moderate response	No response	No response

DAS28 = disease activity score 28; EULAR = European League against Rheumatism.
Am van Gestel et al. Arthritis Rheum 1996;39:34-40.

For ACR20, ACR50 and ACR70 response rates at week 24: Numerically higher rates were seen in the TCZ groups than the placebo+MTX group. The proportion of ACR20 responders at week 24 was 65.2%, 73.6%, 74.2% and 70.2% in the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively.

The proportion of ACR50 responders at week 24 was 43.2%, 47.9%, 56.9% and 47.6% in the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively. The proportion of ACR70 responders at week 24 was 25.4%, 34.7%, 38.6% and 30.1% in the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively. Comparison of TCZ 8 mg +MTX vs placebo+MTX was statistically significant for all three variables at both week 24 and 52 with odds ratio for ACR20, ACR50 and ACR70 at week 24 being 1.57 (95% CI: 1.1,2.3, p=0.014), 1.76 (95% CI: 1.3,2.5, p=0.0009) and 1.87 (95% CI: 1.3,2.7, p=0.0006), respectively.

Exploratory analysis of ACR90 response found it was achieved in 7.0%, 13.9%, 16.6% and 15.1% of the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively.

A major clinical response (MCR) was defined as maintenance of ACR70 response for 24 or more continuous weeks. At week 52 the rate of MCR was 31% in the TCZ 8 mg+MTX group and 22%, 22% and 16% in the TCZ 4 mg+MTX, TCZ 8 mg+placebo and MTX+ placebo groups, respectively.

In an exploratory analysis of the Clinical Disease Activity Index (CDIA)[1] the proportion of patients in remission at week 52 was 13.2%, 22.2%, 24.5% and 20.5% in the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively.

The proportion of patients with radiographic assessments at baseline and week 52 was between 77% and 79% across the treatment groups. Imputation methods used linear extrapolation for those with at least one post-baseline radiograph and 93% of patients were included in the week 52 analysis. The mean change from baseline to week 52 in the modified total Sharp Score (mTSS) was 0.08 in the TCZ 8 mg +MTX and 1.14 in the placebo+MTX groups which was a statistically significant difference in progression of joint damage (p=0.0001). Numerically lower mean changes were also noted for the other TCZ groups. Observed result analysis (with no imputation for missing results) and sensitivity analysis including patients prematurely withdrawn were consistent.

The mean change from baseline to week 52 in the modified Sharp erosion score (mSES) was significantly lower in the TCZ 8 mg+MTX than placebo+MTX group (0.05 vs 0.63, p=0.0006). The mean change from baseline in joint space narrowing (JSN) was lower with TCZ 8mg+MTX (0.03 vs 0.51) but not statistically significant due to the hierarchical chain of statistical testing. The TCZ 8 mg monotherapy group was also found to result in a reduction in joint damage although this was less than the TCZ 8 mg+MTX group and was not statistically significant in the hierarchical testing sequence.

All treatment groups showed a reduction (improvement) in the mean HAQ-DI which was most marked to week 16 and then slowed to week 52. The mean change from baseline to week 52 was significantly greater in the TCZ 8 mg+MTX than placebo+MTX group (-0.81 vs -0.64, difference -0.17, p=0.0024). The result at week 24 was also significant. Other groups were not statistically significant. Categorical analysis found that the proportion of patients with at least a 0.3 change in HAQ-DI was 69.2%, 81.5%, 81.6% and 73.9% in the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively.

The SF-36 health-related quality of life questionnaire mean physical component scores (PCS) increased in all treatment groups by week 24 and this was maintained to week 52. Categorical analysis of improvement (change >5.42 in the PCS) found this occurred in 64.2%, 70.2%, 78.3% and 68.3% of the placebo+MTX, TCZ 4 mg+MTX, TCZ 8 mg+MTX and TCZ 8 mg + placebo groups, respectively. Results on the mental component scores (MCS) were similar between treatment groups with 40.8-53.5% of the patients reporting improved (change >6.33) at week 24.

Subgroup analysis of the primary endpoint DAS28 remission response shows a consistent trend in favour of TCZ 8 mg +MTX over placebo+MTX. Subgroups included serological status, geographic region, sex, age group, race, weight and duration of RA.

> **Comment**: The numbers in some subgroups were too small to draw conclusions in particular Asians, Blacks, and age >75 years.

[1] The Clinical Disease Activity Index (CDAI) is a continuous measure of RA disease activity. It integrates measures of physical examination, patient's global self assessment, and physician's global assessment (CDAI is defined as the sum of TJC [28], SJC [28], Patient's Global Assessment of Disease Activity [cm], and Physician's Global Assessment of Disease Activity [cm]). CDAI scores of >22 are considered indicative of high disease activity, 10.1−22 moderate disease activity, 2.8−10 low disease activity, and <2.8 remission.

Analyses of pre-dose mean ESR and mean CRP found a reduction which was greater in the TCZ 8 mg groups and this was maintained from week 24 to 52.

There were 11 patients who developed neutralising anti-TCZ antibodies during treatment and none of these patients withdrew for lack of efficacy or from a reduction in response after achieving ACR50.

7.1.2. Other efficacy studies

The Sponsor states that supportive efficacy data for TCZ in an early RA population was provided by studies WA17824 and MRA012JP. In addition long term data were available from study WA17823 and its extension. The studies were summarised in the Summary of Clinical Efficacy, the clinical study reports were not submitted in this application as they had been included in previous submissions.

7.1.2.1. Study WA17824

Study WA17824 was a phase III, 24 week randomised controlled non-inferiority study assessing the safety and efficacy of TCZ 8 mg/kg + placebo MTX versus MTX + placebo TCZ, in 572 adult patients with active moderate to severe RA who were MTX-naïve or had not received MTX for 6 months. The primary endpoint was the proportion of patients with ACR20 response at week 24.

Data from the primary analysis at week 24 were evaluated in the tocilizumab submission 2008-0256-3. An exploratory post-hoc analysis of data from the subgroup of 241 patients with early RA (duration of ≤2 years at baseline) was included in the current dossier Summary of Clinical Efficacy. This subgroup included 116 and 125 patients in the TCZ+placebo and placebo+MTX groups, respectively. The demographics of this subgroup were similar to study WA19926 as were the baseline DAS28 and HAQ-DI scores.

In the early RA subgroup, the DAS28 remission response rates at week 24 were 37.1% vs 16.0% in the TCZ 8 mg+placebo and placebo+MTX groups, respectively, with a weighted difference of 22.4% (95% CI: 10.0, 34.7). Response on ACR20/50/70, ACR/EULAR remission and HAQ-DI were also found to be similar to study WA19926.

> **Comment**: While the early RA subgroup analysis was conducted post-hoc, the results were similar to WA19926 and provide some supportive efficacy evidence for TCZ 8 mg/kg monotherapy in this population.

7.1.2.2. Study MRA012JP

Study MRA012JP was conducted by co-development partner Chugai in Japan. It was a 52 week unblinded, randomised study of TCZ 8 mg/kg monotherapy compared to conventional DMARD therapy in 306 patients with active RA who had an inadequate response to conventional DMARDs. It was stated that approximately half the patients had an RA duration of ≤2 years. The primary endpoint was the mean change in the modified Sharp erosion score at week 52. Data provided were on the analysis of the whole study population rather than an early RA subgroup. This Japanese study included patients with more joint degeneration as the mean baseline total Sharp score was 28.3 in the TCZ 8mg/kg group compared to 6.85 in TCZ 8mg+placebo group in study WA19926. Data showed a reduction in radiographic progression in the TCZ 8 mg/kg group compared to DMARD group.

> **Comment**: This study was unblinded and conducted in a different patient population to WA19926 with longer disease duration and more severe joint degeneration. While the data are suggestive of a positive effect on joint damage reduction, given the factors listed the evaluator cannot draw any definitive conclusions on efficacy TCZ 8 mg/kg monotherapy in the early RA population from this study.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The LTE All-Exposure population comprised of data (cut-off date 02 May 2012) pooled from the 5 pivotal RA phase III studies WA17822, WA17823, WA18063, WA17824, and WA18062, the safety study WP18663, the open label LTE clinical studies WA18695, WA18696, and 6-month data from the Phase IV TCZ monotherapy study WA19924. From this pooled population (n=4171), data were assessed for all patients with ≤ 2 years since their RA diagnosis at the time they received their first dose of TCZ ("LTE Early RA subpopulation").

This early RA population consisted of 3165 patient years with a mean and median disease duration of 3.93 and 5.08 years, respectively. Of the 449 patients receiving TCZ treatment at week 264, 35.4% maintained DAS28 remission for 48 consecutive weeks, 26.9% for 96 weeks, 19.8% for 144 weeks and 15.8% for 192 consecutive weeks. For subjects on TCZ monotherapy in study WA17824 there were 96 patients on treatment at week 264 and 26.0% maintained DAS28 remission for 96 consecutive weeks, 17.7% for 144 weeks, and 14.6% for 192 weeks. In the early RA population there were 449 patients on treatment at week 264 with 40.3%, 23.4% and 11.4% who had maintained ACR20, ACR50 and ACR70 response, respectively, for 192 weeks.

> **Comment**: Due to withdrawal of patients who may have had a poor response to treatment, such analysis is of limited benefit in determining long term efficacy.

7.1.4. Evaluator's conclusions on clinical efficacy for early RA

The efficacy of TCZ in the early RA, MTX-naïve population was based on data from study WA19926 which included 1162 predominantly female Caucasian patients with RA ≤2 years (mean duration 0.4-0.5 years) who were MTX-naïve and had moderate to severe disease with a high baseline mean DAS28 (6.6-6.7) but low joint damage (mTSS 5.66-7.72).

The study met its primary endpoint with superior efficacy of TCZ 8 mg/kg +MTX compared to MTX monotherapy demonstrated on DAS28 remission response (DAS <2.6) at week 24(44.8% versus 15.0%; OR = 4.77; p<0.0001). Results were maintained to week 52 and supported by positive results on improvement in ACR20, ACR50 and ACR70 responses and exploratory analyses of EULAR remission. Radiographic joint damage assessment (as measured by the mTSS) found less progression with TCZ 8 mg/kg+MTX than MTX monotherapy and this covered both the erosion score and joint space narrowing components. There was also significant improvement in physical function as measured by the HAQ-DI.

The results for the other two groups, TCZ 4 mg/kg+MTX and TCZ 8 mg/kg monotherapy, were generally numerically superior to MTX monotherapy although not statistically significant on the hierarchical testing to control for multiplicity. The exception to this was that TCZ 8 mg monotherapy had a significantly greater DAS28 remission response than MTX monotherapy.

Data from the previously submitted study WA17824 provided some supportive efficacy evidence for the early RA population treated with TCZ 8 mg/kg monotherapy. The robustness of the data were, however, limited by the fact that it was a post-hoc subgroup analysis. Data from the Japanese study MRA012JP showed some evidence of TCZ monotherapy efficacy on joint damage reduction. The study however was unblinded and in a different population so results are difficult to extrapolate.

Pooled data from previously submitted studies showed some evidence of maintenance of response however these data may be biased due to the potential withdrawal of poor or non-responders. Therefore, the week 104 data from the pivotal study WA19926 needs to be provided for evaluation to better define the longer term efficacy of TCZ in the early RA population.

In relation to the proposed changes to the PI, the data proposed for the *Clinical Trials* section in relation to study WA19926 are acceptable. The efficacy data from study WA19926 support proposed indication of:

ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:

in combination with methotrexate (MTX) in those not previously treated with MTX;

The proposal to include the wording in relation to inhibition of joint damage is less clear cut as, while the comparison to the placebo+MTX was statistically significant, the analysis came after the break in the hierarchical testing sequence used to address multiplicity. Consequently, the result cannot be deemed significant. For this reason the evaluator does not support the changes underlined in the following section of the indication and recommends this information be discussed in the *Clinical Trial* section [of the PI] noting that there was a numerically superior but not statistically significant result.

ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given alone or in combination with methotrexate.

7.2. Other studies included in the dossier

7.2.1. Study WA18695

7.2.1.1. Methods

Study WA18695 was the long term extension for patients completing treatment in study WA17822. The study was a post-approval commitment from submission 2008-0256-3. It was an open label, single group, international multicentre study which enrolled 538 patients (86% from an eligible population of 623) who had completed 24 weeks in the primary study WA17822. The initial patient population were adults with moderate to severe RA with inadequate response to MTX. The study duration was 5 years and it was conducted between August 2005 and May 2012 at 72 sites worldwide. The primary objective was long term safety. Secondary objectives were long term efficacy, reduction in concomitant steroid treatment and effect on biomarkers.

For inclusion subjects needed to be on a stable MTX dose between 10 and 25 mg/week, stable oral corticosteroids (10≤mg/day) and stable NSAIDs. Exclusion criteria were: cell-depleting therapy; IV gamma globulin, plasmaphoresis; immunomodulator therapy; corticosteroids except for oral within 6 weeks; immunisation with live or attenuated vaccine since last treatment in WA17822; treatment with alkylating agents; allergic reactions to monoclonal antibodies; serious uncontrolled medication conditions; active or recurrent infections; active malignancy; AST or ALT ≥3x ULN, BR >2x ULN, neutrophils <1000/mm^3.

All patients received TCZ 8 mg/kg up to a maximum of 800 mg by IV infusion every 4 weeks. Methotrexate was given for the first 48 weeks. Other DMARDs were prohibited before week 48. Anti-TNF, anti-IL-1 therapies as well as T-cell costimulation modulator agents and other biologics were prohibited. Oral CCS ≤10 mg/d were allowed.

It was noted that GCP non-compliance was identified at 2 of the study sites which enrolled 30 subjects. The Sponsor stated that the non-compliance did not affect data validity and so data were included in analyses. Analysis was of all included patients who received at least one dose of TCZ.

7.2.1.2. Results

Of the 538 included patients, there were 353 (65.6%) who received treatment for 264 weeks (approximately 5 years). There were 2461.9 person years exposure with a mean duration of 4.6 years. Twenty percent of patients prematurely discontinued due to safety reasons and 14% for non-safety reasons including insufficient therapeutic response and treatment refusal.

The study population was largely female (82%) and White (72%) with a mean age of 50.8 years. Patients had moderate to severe RA with a mean DAS28 score of 6.5, 56% were on

corticosteroids at baseline and all were on MTX with a mean dose of 14.7 mg/week. The most common concurrent diseases were hypertension (27%), osteoporosis (10%), diabetes (7%), depression (5%) and hypercholesterolaemia (4%). GI disorders were reported in 17% of patients including 4% with dyspepsia, 3% gastritis and 3% GOR disease. Concomitant non-RA medications included PPIs (29%), calcium (22%), ACE inhibitors (14%), beta blockers (12%), calcium channel blockers (7%) and statins (6%). During the study 41% and 20% of patients received oral or parenteral corticosteroids, respectively.

The proportion of patients achieving ACR20/50/70/90 response increased during the first year of treatment and then was maintained over the 5 years. At week 264 the proportions were 84%, 68%, 46% and 19% for ACR20, ACR50, ACR70 and ACR90, respectively. A major clinical response (ACR70 response maintained for at least 6 consecutive months) was achieved in 28.8% of patients after 264 treatment weeks. An ACR70 response which was maintained for 48, 96, 144 and 192 weeks occurred in 21.6%, 17.3%, 13.7% and 9.4% of patients respectively, after 264 weeks of treatment.

The mean DAS28 score decreased during the first 2 years of treatment and then was maintained. At week 264, the DAS28 (<2.6) remission rate was 60.1% and 39.6% of patients had a sustained DAS28 remission of at least 24 weeks. At week 264, EULAR response of good, moderate and no response was 71%, 25% and 4%, respectively. At week 264, a clinically relevant ≥5 point improvement in the SF-36 mental component and physical component occurred in 49.1% and 71.3%, respectively.

For patients achieving a 50% reduction from baseline in TJC and SJC, a reduction of oral corticosteroid dose was allowed. In any 6 month period of the study this occurred in no more than 10% of patients and discontinuation of oral CCS was infrequent (<5% in any 6 month period).

Analysis of serum IL-6 levels found them to be moderately stable from week 48 to 264. Mean ESR and CRP levels decreased to week 48 and then remained stable at this reduced level.

7.2.2. Study NA25256

7.2.2.1. Methods

Study NA25256 was a phase IV, randomised, parallel-group, open-label, 20 week, multicentre study which evaluated the effects of tocilizumab on vaccination in subjects with active rheumatoid arthritis receiving background methotrexate. It was conducted between September 2010 and December 2011 at 35 sites in the US. The study was a post approval commitment to the EMA and US FDA.

The primary objective was to evaluate the humoral immune response 5 weeks after vaccination with 23-valent pneumococcal polysaccharide vaccine (Pneumovax Merck & Co, Inc) in patients with active RA treated with TCZ in combination with MTX, compared with the humoral immune response in patients treated with MTX alone. The primary endpoint for humoral immune response was defined as the proportion of patients with a response to ≥6 of 12 anti-pneumococcal antibody serotypes. Secondary objectives include response to other combinations of the 12 serotypes, response to tetanus toxoid and antibody titres.

Patients were randomised via an IVRS in a 2:1 ratio to either TCZ 8 mg/kg +MTX or MTX alone. Randomisation was stratified by age group (18-50 and 51-<65 years). TCZ treatment was open label and via an IV infusion every 4 weeks for 20 weeks. In the MTX alone group, TCZ 8 mg/kg was commenced at week 8 and given to week 20.

Baseline titres for anti-pneumococcal antibody and anti-tetanus antibody were drawn at week 3, immediately prior to patients being vaccinated with Pneumovax and tetanus toxoid. Anti-pneumococcal and anti-tetanus antibody responses were assessed 5 weeks post-vaccination (week 8). Patients were followed up to week 28. A positive response to pneumococcal vaccine was defined as a 2-fold increase in serum antibody titres or an increase of >1 mg/L from

baseline levels. A positive response to tetanus toxoid vaccine was defined as antibody levels ≥0.2 IU/mL for patients with baseline tetanus antibody level <0.1 IU/mL or a 4-fold increase in antibody levels compared with baseline for patients with baseline tetanus antibody level ≥0.1 IU/mL. Analysis was descriptive. Assuming an 80% response rate, the sample of 60 and 30 patients in the TCZ+MTX and MTX groups, respectively, gave an estimated treatment difference of 0% on the primary endpoint with a 95% CI of -15.8 to 19.1%. Analysis was conducted on observed case data.

Inclusion criteria were ≥18 to <65 years old with a primary diagnosis of RA >6 months duration at baseline according to the revised 1987 American College of Rheumatology criteria. The SJC and TJC was ≥4 at screening. Previous immunisation with pneumococcal polysaccharide and tetanus toxiod vaccines must have been ≥3 years and ≥5 years ago, respectively. MTX was stabilised at 7.5–25 mg/week for at least 8 weeks prior to baseline. All other DMARDs were withdrawn with appropriate washouts. Oral corticosteroids were allowed if dose was stable and <10 mg/day.

7.2.2.2. Results

There were 112 patients screened and 91 randomised (60 and 31 in the TCZ+MTX and MTX groups, respectively). There were 17 premature terminations (18.3% vs 19%) with more due to safety reasons in the TCZ+MTX group (8% vs 0%). The ITT population included 91 patients and, due to 10 protocol violations, the PP population 81 subjects (54 and 27 in the respective groups). Groups were reasonably well balanced on baseline demographic characteristics. The mean RA duration was longer in the TCZ+MTX group (13.2 vs 8.4 years) and mean baseline anti-pneumococcal level was higher (85.9 vs 72.3 mg/dL), median values were however similar.

At 5 weeks post vaccination (week 8), the proportion of patients with response to ≥6 of 12 pneumococcal serotypes was lower in the TCZ+MTX group than the MTX along group (60.0% vs 70.8%) with a difference of -10.8% (95% CI: -33.7, 12.0). The rate of response to vaccine was lower in the older age group (51-<65 years) (56.3% vs 66.7%) with a similarly lower response in the TCZ+MTX groups irrespective of age.

> **Comment**: The achieved response rate was lower than the predicted 80% for sample size calculations.

There were lower proportions of the TCZ+MTX groups responding to serotype combinations. Response to individual serotypes was generally also lower in the TCZ+MTX group. Response to tetanus toxoid vaccination was similarly low in both treatment groups, 42.0% vs 39.1%, respectively (difference 2.9%, 95% CI: -21.4, 27.1).

The mean (SD) change from baseline in anti-pneumococcal antibody levels were 110.2 (188.4) mg/L and 216.1 (261.9) mg/L, in the TCZ+MTX and MTX alone groups respectively. Mean change from baseline in anti-tetanus antibody levels were similar (7 IU/mL in both groups).

Post-hoc analysis of response rates in subjects with above or below the 50th percentile for RA duration (9.3 years) found similar rates of vaccine response. In addition, post-hoc analysis of those on or not on concomitant oral CCS also found similar results.

7.2.3. Evaluator's conclusions on other efficacy data

7.2.3.1. Long term efficacy

WA18695 was the 5 year extension study of WA17822 and included 538 moderate to severe RA patient with 2461.9 person years of exposure. Two thirds of patients completed the 5 years treatment. At 264 weeks, 46% of patients had achieved an ACR70 response and 61% DA28 remission. Overall, efficacy results indicated improvement during the first year of treatment and maintenance of response thereafter. Quality of life data were supportive. Ability to reduce or cease oral corticosteroids due to sustained efficacy was, however, infrequent.

Comment: The study was open label, uncontrolled and efficacy data are subject to bias from analysis only of subjects continuing in the study who are possibly more likely to be treatment responders. It is acknowledged that a retention rate of 66% is acceptable for a 5 year study.

No efficacy data from this study have been proposed for inclusion in the PI.

7.2.3.2. Vaccination

NA25256 was a randomised, parallel-group, open-label, multicenter study to evaluate the effects of tocilizumab on vaccination in 91 subjects with active RA receiving background MTX. A positive immune response (≥2-fold or >1 mg/L increase in the titre concentration of at least 6 anti-pneumococcal antibody serotypes) to Pneumovax 23-valent polysaccharide vaccine was lower in subjects receiving TCZ and MTX compared to MTX alone (60 vs 71%) although the confidence interval of the difference in response rates crossed zero. Response was lower in older patients 51 to <65 years (56% vs 67%) but the difference between treatment groups remained similar. Immune response to tetanus toxoid was similar between groups (39% vs 42%).

From this study the Sponsor has proposed an addition to the PI as underlined below:

Vaccinations

Live and live attenuated vaccines should not be given concurrently with ACTEMRA as clinical safety has not been established.

No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

In a randomised open-label study, adult RA patients treated with ACTEMRA and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients receiving MTX only.

It is recommended that all patients, particularly sJIA patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating ACTEMRA therapy. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents

Comment: The results indicated that only 60% of patients receiving TCZ+MTX can mount an adequate immune response to Pneumovax and that the response is numerically poorer that with MTX alone. The evaluator recommends that it be made clearer to prescribers that, while immunisation is certainly recommended, a substantial proportion of patients may not mount an adequate immune response to vaccination. The proposed sentence should therefore be reworded. Clearly it is desirable that immunisations need to be up to date with vaccination undertaken prior to commencing TCZ.

8. Clinical safety

8.1. Studies providing evaluable safety data

The Sponsor proposed a change of indication of TCZ to include adult patients with severe, active and progressive rheumatoid arthritis not previously treated with methotrexate. For this the pivotal study was WA19926. In addition, safety data from the submitted open label extension

study WA18695 in patients with moderate to severe RA and inadequate response to MTX are discussed in Section 8.2.

- Pivotal efficacy study (early RA)

  In the pivotal efficacy study WA19926, the following safety data were collected:

  - General adverse events (AEs), SAEs and discontinuations due to AEs.
  - AEs of particular interest, including malignancies, myocardial infarction, stoke, elevated lipids, infection, anaphylaxis/serious hypersensitivity[2] and infusion reactions, GI perforations, demyelinating disorders, serious bleeding events, thrombocytopaenia, hepatic events and elevated liver enzymes.
  - Laboratory tests, including haematology, blood chemistry, serum lipids, liver profile; acute phase reactants (ESR at local laboratory).
  - Vital signs
  - Immunogenicity with anti-TCZ specific blocking and neutralising antibodies in those positive on the screening assay.

- Pooled safety data
  - Pooled safety data from 3 placebo controlled phase III studies (WA17822, WA17823 and WA18063) in patients with inadequate response to DMARDs to allow comparison of safety data to WA19266 (Controlled DMARD-IR population). This included treatment to 24 weeks in 2 studies and to 52 weeks in one study.
  - Long term extension studies (LTE all exposure population). This included data from: five pivotal phase III studies (WA17822, WA17823, WA18063, WA17824 and WA18062); safety study WP18663; open label LTE clinical studies WA18695, WA18696, and WA17823 extension; and 6 month data from phase IV monotherapy study WA19924. This population included 4171 patients with 16,204.8 person years exposure.
  - Two subpopulations: MTX naïve or not received MTX within 6 months (LTE MTX-naïve subpopulation) and ≤2 years since RA diagnosis (early RA population).
  - TCZ monotherapy patients from WA17824 (LTE TCZ monotherapy subgroup).

- Other post-marketing data

The Summary of Clinical Efficacy also included a retrospective epidemiological survey of US health claims using Thomson Reuters MarketScan database. The report was dated 15 April 2013. The study objectives were to estimate the incidence of specific events of interest in early RA patients treated with biologics. Early RA was defined as a new occurrence of RA with follow up restricted to 2 years after RA first diagnosis. The endpoints of interest were acute hepatic events, cardiovascular events, serious infections, serious bleeding event and malignancies.

AE data for deaths, SAEs, AEs leading to withdrawal and of special interest were presented as rates per 100 person years (PY) due to differing treatment durations.

8.2. Studies that assessed safety as a primary outcome – WA18695

Study WA18695 was a phase III open label, single group, international, multicentre, 5 year extension study of the 24 week phase III randomised controlled trial WA17822 (see also Section 7.2.1). The primary objective was to assess long term safety of 8 mg/kg TCZ with regard to AEs and laboratory parameters.

[2] Serious hypersensitivity was defined as all SAEs reported during or within 24 hours of the injection/infusion, which were considered by the investigator to be at least remotely treatment-related.

There were 538 patients who received at least one dose of TCZ with a total exposure of 2461.9 person years and a median of 5.37 (range 0.2 to 6.4 years). The AE rate was 275.7 events per 100 person years (PY). This rate was higher in the first 12 months (393.8 per 100 PY) and then relatively constant over years 2 to 5 years. The most frequent AEs were in the infections/infestation SOC (84.2 per 100 PY).

There were 10 deaths with a rate of 0.41 events per 100 PY. Four were cardiac (three MI and one AV block/cardiac failure), two infections (pneumonia, mediastinitis/pneumonia), two GI metastatic cancers (colon and gastric), one haemorrhagic stroke and one pulmonary embolism.

There were 341 SAEs with a rate of 13.9 per 100 PY. The most commonly involved SOCs were infections/infestations, neoplasms and GI disorders. The most frequent events were pneumonia (rate of 0.49 per 100 PY), osteoarthritis (rate of 0.28), cellulitis, diverticulitis, gastroenteritits and cholecystitis (rate of 0.2 each).

AEs leading to premature discontinuation occurred in 103/538 patients (19%) with a rate of 4.2 per 100 PY. Events were most commonly in the neoplasms SOC followed by infections, investigations and GI disorders. There were 9 (1.7%) subjects who withdrew due to elevated transaminases.

The rate of infections was relatively constant over each year of the 5 year time period (87-93 per 100 PY years 1 to 4 and 72 per 100 PY at >48 months). The serious infection rate was 3.6 per 100 PY with the most frequent being pneumonia (2 cases were fatal). There were 4 patients with 5 opportunistic infections (rate of 0.2): 3 events of oesophageal candidiasis (in 2 patients); 1 anal fungal infection; and 1 mycobacterial infection (species not known). All cases were non-serious. There were 7 events in 6 patients with tuberculosis (0.3 events per 100 PY) with 4 being serious (0.16 per 100 PY).

The rate of hypersensitivity AEs[3] was 9.1, with a higher rate in the first year (27.4) which decreased to 4.1 in the >48 month period. Of the 244 events, 7 were serious (0.3 per 100 PY) – pneumonia, respiratory tract infection, breast cancer, metastatic SCC, melaena, interstitial lung disease and hypertension. There were no cases of anaphylaxis.

There were 536 patients (99.6%) screened for anti-TCZ antibodies with 4 patients (0.7%) testing positive on the confirmation assay. The rate of neutralising antibodies was also 0.7%. There were no patients with insufficient therapeutic response or loss of efficacy who were antibody positive.

The rate of hepatic evens was 0.7 per 100 PY (17 events) all of which were non-serious and the most common was hepatic steatosis (12 events at 0.5 per 100 PY). There was one event which led to discontinuation and one to dose modification.

The rate of myocardial infarction (MI) was 0.4 with 7 of 9 events being serious and 3 of these fatal. The rate of stroke was also 0.4 with 3 of 9 events being serious. There were 4 cardiovascular deaths with a rate of 0.2 per 100 PY (95% CI: 0.04, 0.42). There were 7 events (0.2 per 100 PY) identified of GI perforation, 6 of which were serious. Three of the events (rate 0.12 per 100 PY) were confirmed on medical review as gross perforations (one oesophageal and two diverticular). The rate of malignancy and serious malignancy was 1.3 and 1.1, respectively. The most frequent malignancies were breast, lung/bronchus and NMSC. The SMQ for demyelination and neuropathy identified one case of monoclonal hypergammaglobulinaemia (0.04 per 100 PY). There were 13 serious bleeding events in 12 patients (0.5 per 100 PY). One case was fatal (haemorrhagic stroke), 2 led to discontinuation (rectal haemorrhage, melaena) and 5 to dose modification.

[3] Hypersensitivity event was defined as any AE occurring during or within 24 hours of an infusion which was not deemed "unrelated" to treatment by the investigator. Clinically significant events were those that led to withdrawal.

The mean neutrophil count decreased and remained stable toward the lower level of the normal range. The rate of grade 1, 2, 3, and 4 neutropaenia was 21.7%, 18.2%, 4.6% and <1%. Two patients discontinued due to decreased ANC. Platelets similarly decreased to the lower level of the normal range and then remained stable. The rate of grade 1, 2, 3, and 4 thrombocytopaenia was 18.4%, 1.3%, <1.0% and 0%. There were no discontinuations due to low platelets and no cases with associated serious bleeding events.

Both mean ALT and mean AST were noted to increase by week 2 then remain relatively stable at the upper limit of normal. Most of the shifts were within the range of >ULN to 3xULN. No cases met Hy's Law definition. There were 8 patients withdrawn for liver enzyme changes with 6 of these occurring in the first 12 months of treatment. Increases in lipids (cholesterol, LDL, HDL and TG) were noted and the proportion of patients with LDL ≥130 mg/dL increased from 24% at baseline to 70% by months 13-24.

The proportion of patients in JNC 7 hypertension categories at baseline and after 5 years treatment increased in prehypertension (41.8% to 50.8%) and remained stable in Stage I (18.5% to1.4.4%) and Stage II (4.1% to 2.7%).

8.3. Patient exposure

In study WA19926, there were 282 patients in the placebo+MTX group and 871 in the TCZ (4 and 8 mg) +MTX or TCZ monotherapy groups (Table 3). Data were included up to week 52 and the mean exposure was similar between groups at 0.87-0.89 years. As mean actual exposure to TCZ was 87-89% of all possible doses, this corresponded to a actual exposure per group of 249-261 PY and a total exposure for the all-TCZ group of 794.9 patient years (Table 4).

Table 3: Exposure by treatment group. Study WA19926

Pooled Treatment Group	N	Patient Years Duration	Individual Study Treatment Arms Included
Placebo+MTX	282	254.9	WA19926 placebo+MTX
All-TCZ	871	794.9	WA19926 TCZ 4 and 8 mg/kg
TCZ 4 mg/kg+MTX	289	263.8	WA19926 TCZ 4 mg/kg+MTX
TCZ 8 mg/kg+MTX	290	262.6	WA19926 TCZ 8 mg/kg+MTX
TCZ 8 mg/kg monotherapy	292	268.5	WA19926 TCZ 8 mg/kg+placebo

Table 4: Extent of actual exposure to IV TCZ (or placebo) trial treatment (WA19926 Safety population)

	PLACEBO + MTX (N=282)	TCZ 4 MG/KG + MTX (N=289)	TCZ 8 MG/KG + MTX (N=290)	TCZ 8 MG/KG + PLACEBO (N=292)
Extent of Exposure (years)				
n	282	289	290	292
Mean	0.88	0.88	0.87	0.89
SD	0.254	0.240	0.261	0.237
SEM	0.015	0.014	0.015	0.014
Median	1.00	1.00	1.00	1.00
Min-Max	0.1 - 1.0	0.1 - 1.0	0.1 - 1.0	0.1 - 1.0
Total Patient Years Exposure to IV Treatment	249.2	255.6	253.2	260.6

Extent of exposure = (date of last IV dose within the treatment group + 28 days) minus date of first IV dose within the treatment group + 1 day.
Total patient years exposure is the sum of the exposure to IV across all patients.

Exposure in the controlled DMARD-IR population was 1268.2 PY in the pooled TCZ 4 mg and 8 mg/kg groups. Exposure in the LTE all exposure population was 16205 PY with 1749 PY and 3165 PY in the MTX naïve and early RA subpopulations, respectively. In study WA19824, the mean duration of TCZ 8 mg/kg montherapy was 4.9 years with 659 PY exposure.

The demographic characteristics of the safety populations are shown in Table 5. Patients had severe disease, while disease duration and previous DMARD use varied.

Table 5: Summary of key baseline demographic and RA disease characteristics

	Study WA19926		Long Term Extension Data from IV TCZ Studies		
	Placebo+MTX N=282	Range of Values Observed in the 3 Active TCZ Treatment Groups N=288–292	All-TCZ N=4171	MTX-Naïve N=417	Early RA N=805
Sex					
Male (%)	20	21 – 25	18	20	21
Female (%)	80	75 – 79	82	80	79
Mean Age in Years	49.6	49.5 – 51.2	52.1	50.7	49.5
Mean Weight in kg	74.14	73.90 – 75.02	73.5	73.8	75.3
Race (%)					
White (%)	77	76 – 79	75	73	75
Mean Duration of RA (years)	0.4	0.4 – 0.5	9.23	5.37	1.12
Mean Number of Previous DMARDs/ anti-TNFs [a]	0.2	0.2 – 0.3	1.9	0.5	0.9
Oral Corticosteroid Use					
Yes (%)	38	33 – 40	58	41	53
No (%)	62	60 – 67	42	59	47
Mean Baseline DAS28 Score	6.6	6.7 – 6.7	6.4	6.1	6.2

The n for different analyses may vary slightly.
Data for WA19926 are based on ITT population, data from LTE studies are based on Safety population.
[a] Anti-TNFs were only allowed in LTE population.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal study

In WA19926, AEs were frequent (83.3% - 88.6%) and the rate of at least one AE over 52 weeks of treatment was higher with TCZ treatment: 423.9 vs 405.7 per 100 PY in the all TCZ and placebo+MTX group, respectively. The rate of AEs was 434.1, 444.3 and 394.1 in the TCZ 8 mg/kg+MTX, TCZ 4 mg/kg+MTX and TCZ 8 mg/kg+placebo groups, respectively.

The highest AE rate was in the infection/infestation SOC followed by the GI disorders and investigations. The most frequent AEs were nausea, URTI, increased ALT, nasopharyngitis and increased transaminases. The rate of increased ALT and increased transaminases was highest with the TCZ and MTX combination.

The rate per 100 PY for mild, moderate and severe AEs was similar between the all TCZ and placebo+MTX groups: 267.2 vs 259.3, 143.2 vs 133.0, and 13.6 vs 13.3, respectively.

8.4.1.2. Other studies

Comparison of AE rates per 100 PY between study WA19926 and the other populations:. The rate of AEs in WA19926 was slightly higher than in the DMARD-IR population and the LTE all exposure populations. In the all exposure population, rates for the initial 6 months of treatment and the period of 7-12 months indicated some decline in AE rates with time. The rates in this population for 1 year of treatment were somewhat more comparable to the WA19926 study TCZ population (423.9 events per 100 PY).

AE rates in the early RA and MTX naïve subpopulations were also lower that those found in study WA19926 (288 and 272 vs 434 events per 100 PY). Comparison of events rates in TCZ monotherapy found higher rates in WA19926 than WA17824 LTE (394 vs 254 per 100 PY)

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal study

The proportion of patients with treatment-related AEs was higher with the combination (TCZ 4mg+MTX: 88.6% and TCZ 8mg+MTX: 88.3%) than with monotherapy TCZ (85.6%) or placebo+MTX (83.3%). The rate per 100 PY of treatment-related AEs was 225.8, 232.0, 182.9 and 164.0 in the TCZ 8 mg/kg+MTX, TCZ 4 mg/kg+MTX, TCZ 8 mg/kg+placebo and placebo+MTX groups, respectively. Treatment-related AEs were most frequently in the SOCs of infections/infestations followed by GI disorders and investigations. The most frequently occurring treatment-related AEs in the TCZ 8 mg/kg+MTX group were increased ALT, transaminases increased, AST increased, nausea, URTI, bronchitis, nasopharygitis and mouth ulceration.

8.4.2.1.1. Other studies

Data on treatment-related AEs in the pooled safety populations were not provided.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Deaths

There were 9 deaths were reported in study WA19926, 2 in the placebo+MTX and 7 in the all-TCZ group, with similar rates between treatment groups. Infections, particularly pneumonia were involved in 6 of the 9 cases and 3 patients were aged over 80 years.

The death rate in WA19926, all TCZ and placebo+MTX groups, was higher than in the other pooled populations including the early RA subpopulation (all TCZ 0.88 vs 0.54 early RA subpopulation). In the all exposure LTE population, the most frequent cause of death was infections followed by cardiac disorders and malignancies. The death rate in the TCZ monotherapy group of WA19926 was lower than in the monotherapy group in WA17824 (0.37 vs 0.76).

The Sponsor provided data from a literature review on death rates in early RA patients treated with biologics in randomised controlled trials. The reported mortality rates were between 0.3 and 0.83 events per 100 PY.

8.4.3.2. SAEs

The rate per 100 PY of SAEs in WA19926 was higher with TCZ+MTX combination (13.3 TCZ 8 mg/kg+MTX and 15.9 TCZ 4 mg/kg+MTX) than with TCZ 8 mg/kg+placebo (10.4) or

placebo+MTX group (10.6). The most frequent SAEs were infections/infestations (3.6 vs 2.4 all TCZ vs placebo+MTX).

The rates of SAEs in WA19926 in subjects treated with TCZ were in line with pooled population data including the early RA and MTX-naïve subpopulations. The rate of SAEs in TCZ monotherapy patients was higher in study WA17824 LTE than WA19926 (14.9 vs 10.4). The literature data summarised by the Sponsor reported SAEs rates in early RA patients treated with biologics ranging between 9.3 and 19.7 per 100 PY.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal study

Withdrawal due to an AE was notably higher in patients treated with TCZ 8 mg/kg+MTX than the other groups (20.3% vs7.4-12.1%). The rates per 100 PY were 22.5, 13.3, 12.7 and 8.2 in the TCZ 8 mg/kg+MTX, TCZ 4 mg/kg+MTX and TCZ 8 mg/kg+placebo and placebo+MTX groups, respectively. In TCZ treated patients, the most common AEs leading to withdrawal were in the investigations SOC namely ALT increased, transaminase increased and AST increased.[4] The rate of TCZ-treated patients with liver enzyme elevations was 7.3 compared to 0.8 in the placebo+MTX group.

The proportion of patients with an AE within 24 hours of infusion that led to study withdrawal was 3.1%,1.0 %, 2.4% and 0% in the TCZ 8 mg/kg+MTX, TCZ 4 mg/kg+MTX and TCZ 8 mg/kg+placebo and placebo+MTX groups, respectively. Of these 19 patients, 9 had liver enzyme elevations, 1 neutropaenia and 9 hypersensitivity reactions 2 of which were SAEs.

The proportion of patients with an AE leading to treatment dose modification or interruption was high across all groups: 59.0%, 52.9%, 43.8% and 47.5% in the TCZ 8 mg/kg+MTX, TCZ 4 mg/kg+MTX and TCZ 8 mg/kg+placebo and placebo+MTX groups, respectively. The most common reasons were in the investigations SOC (liver enzyme elevation) followed by infections/infestations and gastrointestinal disorders.

8.4.4.2. Other studies

Withdrawals due to AEs were more frequent in TCZ-treated patients and occurred at a higher rate in study WA19926 (16.1 per 100 PY) than in other populations including the MTX-naïve (4.2 per 100 PY) and early RA (4.7 per 100 PY) subpopulations. This was also the case in the TCZ 8mg/kg monotherapy group of WA19926 compared to the TCZ 8 mg/kg monotherapy population from WA17824(12.7 vs 2.9 per 100 PY).

> **Comment**: The Sponsor stated that this higher rate in WA19926 could have been due to the protocol-specified criteria in relation to elevation of liver enzymes which were not specified in other studies.

8.5. Adverse events of special interest

8.5.1. Pivotal study

Table 6 summarises AEs of special interest.

4 Protocol-specified criteria required withdrawal if:

- The dose of oral (MTX or placebo) study drug had to be reduced to fewer than 3 capsules, or if seven consecutive doses were missed.
- Three consecutive doses of IV study drug were missed because of ALT or AST elevations.
- ALT or AST were increased >5 × ULN.
- ALT or AST were increased ≥3 × ULN and total bilirubin increased >2 × ULN.

Table 6: Overview of Adverse Events of Special Interest

Safety Parameter	Placebo + MTX N = 282	TCZ 4 mg/kg + MTX N = 289	TCZ 8 mg/kg + MTX N = 290	TCZ 8mg/kg + placebo N = 292
Infections (All), n (%)	136 (48.2)	155 (53.6)	137 (47.2)	138 (47.3)
Rate of infections (All) (rate per 100-PY [95% CI])	100.4 (88.5, 113.5)	119.0 (106.2, 133.0)	94.0 (82.7, 106.5)	100.9 (89.3, 113.7)
Serious Infections, n (%)	6 (2.1)	11 (3.8)	10 (3.4)	8 (2.7)
Rate of Serious Infections (rate per 100-PY [95% CI])	2.4 (0.9, 5.1)	4.2 (2.1, 7.5)	3.8 (1.8, 7.0)	3.0 (1.3, 5.9)
GI Perforations (SAEs), n (%)	1 (0.4)	0	0	0
Demyelination (SAEs), n (%)	0	0	0	0
Hepatic Events SOC (SAEs), n (%)	0	0	0	0
Myocardial infarction (SAEs), n (%)	0	3 (1.0)	1 (0.3)	1 (0.3)
Stroke (SAEs), n (%)	2 (0.7)	2 (0.7)	0	0
Malignancies (SAEs)	3 (1.1)	4 (1.4)	1 (0.3)	2 (0.7)
Anaphylaxis/Hypersensitivity (SAEs), n (%)	0	1 (0.3)	0	1 (0.3)
Bleeding Events (SAEs), n (%)	1 (0.4)	2 (0.7)	2 (0.7)	1 (0.3)

n: number of patients with at least one AE

Infections: The rate per 100 PY of infections was slightly higher in the TCZ 4 mg+MTX group than other groups, while the rate of serious infections was highest with both TCZ+MTX combinations (4mg/kg: 4.2, 8 mg/kg: 3.8) compared to the TCZ 8mg/kg monotherapy (2.7) or MTX monotherapy groups (2.4). The incidence of infections was stable over 12 week time intervals during the study. The most frequent infections were URTI, nasopharyngitis and UTI. The serious infection rate was higher in the all TCZ than placebo+MTX group (3.6 vs 2.4) and serious infections were most frequently pneumonia and cellulitis. There were no opportunistic infections and one case of TB (TCZ 8 mg/kg+MTX). Three of the 35 serious infection cases had grade 1 neutropaenia within 30 days of the event. As stated earlier, there were 5 deaths with infection as the cause plus a pneumothorax with underlying pneumonia, these occurred across the treatment groups. Infection was the most frequent reason for withdrawal and second most frequent reason for dose modification/interruption.

Anaphylaxis, hypersensitivity[5]: Hypersensitivity rates were higher in TCZ treated patients 17.6%, 20.4%, 15.4% and 13.8% in the TCZ 8 mg/kg+MTX, TCZ 4 mg/kg+MTX and TCZ 8 mg/kg+placebo and placebo+MTX groups, respectively. Events were most commonly nausea, diarrhoea and ALT or AST elevations. There was one case of anaphylaxis in a patient who received TCZ 4mg/kg+MTX (second infusion) and one case of an infusion reaction in a patient who received TCZ 8 mg/kg+placebo (13th infusion). Both patients were withdrawn.

Malignancy: There were 13 malignancy cases in WA19926, 3 (1.0%) in the TCZ 8 mg/kg+MTX, 3 (1.0%) in TCZ 8 mg/kg+placebo, 4 (1.4%) in TCZ 4 mg/kg+MTX, and 3 (1.1%) in the placebo+ MTX group. Three events were non-serious.

Serious bleeding: There were 6 serious bleeding events 2 (0.7%) in the TCZ 8 mg/kg+MTX, 1 (0.3%) in the TCZ 8 mg/kg+placebo, 2 (0.7%) in the TCZ 4 mg/kg+MTX group and 1 patient (0.4%) in the placebo+MTX group. There were two GI haemorrhages (TCZ 8 mg+MTX and placebo+MTX groups) and one cerebral haemorrhage (TCZ 4 mg+MTX group).

[5] Hypersensitivity event was defined as any AE occurring during or within 24 hours of an infusion which was not deemed "unrelated" to treatment by the investigator. Clinically significant events were those that led to withdrawal.

8.5.2. Other studies

The infection rate in WA19926 was in line with the DMARD-IR population but slightly higher than in the MTX-naïve and early RA subpopulations. Analysis of infection rates in the MTX-naïve subpopulation at 0-6 months (99.9) and 7-12 months (106.6) was comparable to the rate in WA19926 all TCZ group (104.7). There was a similar finding for the early RA subpopulation. The serious infection rate was consistent with other pooled data.

Hypersensitivity, serious hypersensitivity and anaphylaxis rates in the all TCZ group of WA19926 were consistent with pooled data.

Malignancy rates in TCZ-treated subjects in WA19926 (1.3 per 100 PY) were also consistent with the pooled trial data. The rate of malignancy in early RA studies of biologics was summarised from the literature by the Sponsor. This listed rates for all malignancy per 100 PY in the range of 0.39 to 1.9.

Serious myocardial infarction (MI) rates in WA19926 were slightly higher than pooled population data but the number of events was low. Rates of serious stroke were comparable.

The rates of serious bleeding events in the all TCZ group of WA19926 was 0.6 compared to 0.4 and 0.35 per 100 PY in the MTX-naïve and early RA subpopulations.

Unblinded medical review was used to identify cases of gastrointestinal perforation in study WA19926 and this located one case in the placebo+MTX group (rate 0.4). The reported rate in pooled data was <0.3 events per 100 PY.

There were no serious AEs classed as a demyelinating disorder in WA19926 and 3 reported in the LTE all exposure population with none in the MTX naïve or early RA subpopulations. Hepatic events are discussed in Sections 8.6.1.1 and 8.8.1.

8.6. Laboratory tests

8.6.1. Liver function

8.6.1.1. Pivotal study

In WA19926 there was an increase in mean ALT during the first 16 weeks which was most marked in the TCZ 8mg/kg+MTX group. The rate of shift from normal at baseline to >ULN to ≤3xULN in ALT was 48.6%, 35.6%, 39.1% and 36.9% in the TCZ 8 mg/kg+MTX, TCZ 8 mg/kg+placebo, TCZ 4 mg/kg+MTX and placebo+MTX groups, respectively. A shift in ALT from normal to >3xULN occurred in 12.8% of the TCZ 8mg/kg+MTX group. The incidence of worst NCI CTCAE grades for ALT found no cases of grade 4 and 3.4-3.5% of patients with grade 3 ALT elevation in the TCZ+MTX groups. The findings for AST followed a similar trend to ALT. A shift to higher bilirubin was less frequent but still greater with TCZ treatment. Shifts in bilirubin from normal at baseline to >ULN to ≤3xULN occurred in 13.8%, 8.9%, 6.2% and 2.8% of the TCZ 8 mg/kg+MTX, TCZ 8 mg/kg+placebo, TCZ 4 mg/kg+MTX and placebo+MTX groups, respectively. In TCZ treated patients, most bilirubin elevations were grade 1, with 1.4-4.8% with grade 2 increase, 0.3%-0.7% with grade 3 increase and no cases of grade 4 increase.

8.6.1.2. Other studies

Further comparative data on liver function are discussed in Section 8.8.1.

8.6.2. Kidney function

8.6.2.1. Pivotal study

Changes in renal function were unremarkable with no differences between groups noted in study WA19926.

8.6.2.2. Other studies

Pooled data on renal function was not provided.

8.6.3. Other clinical chemistry

8.6.3.1. Pivotal study

In WA19926 there was an increase in mean fasting total cholesterol (TC) to week 8 that was greater in TCZ treated patients and appeared dose dependent. The mean change from baseline to week 52 was 0.78, 0.88, 0.41 and 0.18 mmol/L in the TCZ 8 mg/kg+MTX, TCZ 8 mg/kg+placebo, TCZ 4 mg/kg+MTX and placebo+MTX groups, respectively. Similarly, the mean change from baseline in LDL cholesterol was 0.45, 0.54, 0.19 and 0.12 mmol/L in the respective groups. A shift from LDL level of <160 mg/dL at baseline to ≥160 mg/dL at last observation was more frequent with TCZ treatment and the rate of markedly high LDL (>5.4 mmol/L and increase of ≥30%) was 5%, 7%, 2% and <1% in the respective groups.

For patients not on lipid lowering agents at baseline, the rate of initiation of such medication during the 52 week trial was 5.2%, 7.5%, 3.5% and 3.9% in the TCZ 8 mg/kg+MTX, TCZ 8 mg/kg+placebo, TCZ 4 mg/kg+MTX and placebo+MTX groups, respectively.

8.6.3.2. Other studies

The trend for increase in lipids was seen in the DMARD-IR and LTE all exposure populations and data from WA19926 appeared consistent with these populations.

8.6.4. Haematology

8.6.4.1. Pivotal study

In WA19926 there was a decrease in mean neutrophil which was greatest with the TCZ 8 mg/kg+MTX and TCZ 8mg/kg+placebo groups. In the TCZ 8 mg/kg groups, most changes in neutrophils were grade 1 or 2 (12.3-17.9%) with grade 3 changes in 2.7-3.4% and grade 4 in 0.3%. The incidence of neutropaenia AEs was 1.1% in placebo+MTX, 2.1% in TCZ 4 mg/kg +MTX, 2.4% in TCZ 8 mg/kg+MTX, and 4.1% in TCZ 8 mg/kg+placebo groups.

Mean platelet counts decreased in all TCZ groups and changes were generally grade 1 (6.6-8.6%) with grade 2-4 changes in ≤1%. There were 6 patients with AEs (5 treated with TCZ) of thrombocytopaenia, none of which was associated with serious bleeding.

8.6.4.2. Other studies

In the LTE all exposure population, mean neutrophil counts also decreased and the rate of CTC grade 1, 2, 3 or 4 neutropaenia was 21.6%, 18.2%, 5.4% and <1%, respectively. The rate of grade 1, 2, 3 and 4 decreases in platelets was 17.1%, 1.3%, <1% and <1%, respectively.

8.6.5. Vital signs

8.6.5.1. Pivotal study

There were no notable findings on DBP, SBP or heart rate.

8.6.5.2. Other studies

It was reported that there were no clinically significant changes in BP parameters in the LTE all exposure population.

8.7. Post-marketing experience

Post marketing data are available since initial market approval in April 2005 in Japan. The estimated cumulative exposure is 184,398 patients. In the last PSUR (April 2013 to October 2012) the most frequently reported events were in the SOC of infections/infestation followed by

general disorders and GI disorders. The Sponsor reported that no new safety signals were identified and no changes to the product labelling were warranted.

8.8. Safety issues with the potential for major regulatory impact

8.8.1. Liver toxicity

In WA19926, mean ALT, AST and bilirubin were noted to increase across treatment groups with bilirubin remaining within normal range and transaminases increasing more notably. Most increases of AST and ALT were between the ULN to ≤3x ULN however in the TCZ groups the rate of ALT increase to 3 to >5x ULN was 3.4%-9.7% and to >5xULN in1.4%-3.1%. The most pronounced effect was in the combination of TCZ 8 mg/kg+MTX. There were however no serious hepatic events. There was one case meeting Hy's Law definition (ALT or AST >3x ULN and BR >2xULN) reported in a patient on MTX. Raised transaminases were the major cause of premature termination particularly in the TCZ 8 mg/kg+MTX group and this occurred at a higher rate than reported in the pooled data (6.5% vs 2.5% in the LTE all exposure population).

ALT increase >3xULN generally occurred on only one occasion and the rate of multiple (≥2) elevations (consecutive and non-consecutive), occurred in less frequently: 7.6%, 1.0%, 2.7% and 0.8% of the TCZ 8 mg/kg+MTX, TCZ 8 mg/kg+placebo, TCZ 4 mg/kg+MTX and placebo+MTX groups, respectively. Elevations in AST at multiple time points were less frequent with this occurring in 1.4% of the TCZ 8 mg/kg+MTX group.

While the findings of WA19926 were consistent with presented pooled population data where transaminase increase was also noted, the rate of increased ALT >3xULN in the TCZ 8 mg/kg+MTX group in WA19926 was higher than that reported in the DMARD-IR population TCZ 8 mg/kg+ DMARD/MTX (12.8% vs 5.8%). There were no serious hepatic events in the DMARD-IR population and 7 in the LTE data (rate of 0.04 per 100 PY).

8.8.2. Haematological toxicity

See Section 8.6.4.

8.8.3. Unwanted immunological events

In WA19926, immunogenicity testing was conducted at baseline, week 52 or on study exit. Samples were also collected from patients with infusion reactions. Positivity required antibody detection in the screening and confirmation assays post baseline and negative confirmation assay at baseline. A neutralising assay was performed on samples positive on the confirmation assay. This strategy was reportedly the same as in previous placebo-controlled studies with IV TCZ.

In WA19926, the proportion of patients with anti-TCZ antibodies was 1.4%, 1.1% and 2.2% in the TCZ 8 mg/kg+MTX, TCZ 8 mg/kg+placebo, TCZ 4 mg/kg+MTX groups, respectively compared to 3.2% in the placebo+MTX group. The rate of neutralising anti-TCZ antibodies was 1.0%, 1.0% and 1.7% in the respective active groups.

> **Comment**: The Sponsor reported that the false positive results in the placebo group were consistent with previous studies.

The two patients with anaphylaxis and serious hypersensitivity were not antibody positive. There were 2 of the 19 patients with hypersensitivity AEs who were antibody positive: one with an infusion reaction and one with muscle spasms (who was also antibody positive at baseline). There were 11 patients who were neutralising antibody positive (3 were false positives at baseline) but none were classed as having loss of efficacy or withdrew due to insufficient response to therapy.

> **Comment**: There were also an additional three subjects who were neutralising antibody positive with a negative confirmation assay.

In the small number of patients who were anti-TCZ positive (n=13) there was no reported effect on TCZ concentration reduction.

Data from DMARD-IR studies reported anti-TCZ antibody development in 0 to 3.5% of patients. In the LTE all exposure population, the reported positivity rate was 1.1% (44/3945) on the confirmation assay. Five of the 44 seropositive patients had an anaphylactic reaction.

8.9. Other safety issues

8.9.1. Safety in special populations

There were 7 pregnancies in WA19926 3 in the TCZ 8 mg/kg+MTX group and 4 in the TCZ 8 mg/kg+placebo group. The outcomes were: 2 spontaneous abortions, 2 elective abortions and 3 were ongoing. In the LTE all exposure population there were 48 reported pregnancies, 44 with known outcome of which 18 had terminations, 10 spontaneous abortions, 1 a trophoblastic tumour, 14 deliveries at term and 1 premature delivery. Of the live births, 1 died of acute respiratory distress and 1 had left kidney pelviectasis. Some of these women were also taking MTX.

The safety of TCZ monotherapy in early RA patients in WA19266 was compared to the LTE monotherapy subpopulation. The AE rate and AE withdrawal rates were higher however the SAE and death rates were lower in study WA19926 than in the LTE monotherapy population. Comparison of the rates of death and AEs special interest between the two groups shows similarity.

8.10. Evaluator's overall conclusions on clinical safety

8.10.1. Early RA population

Study WA19926 assessed the safety of TCZ in 871 early RA patients who were MTX naïve over 52 weeks with 73-76% of these patients receiving all scheduled infusions. The total exposure to TCZ was 794.9 patient years.

In general, patients treated with the higher TCZ dose of 8 mg/kg in combination with MTX had a higher rate of AEs, discontinuations due to AEs and death. The SAE rate was however more similar between treatment groups (Table 7) and the number of deaths were low (n=9) making intergroup comparisons of death rates difficult.

Table 7: Study WA19926 Adverse Events

	No. of Patients (%)			
Type of Events	Placebo +MTX N=282	TCZ 4 mg/kg +MTX N=289	TCZ 8 mg/kg+ MTX N=290	TCZ 8 mg/kg+ placebo N=292
At least one AE	235 (83.3)	256 (88.6)	256 (88.3)	250 (85.6)
Serious AE	24 (8.5)	29 (10.0)	31 (10.7)	25 (8.6)
Deaths	2 (0.7)	4 (1.4)	2 (0.7)	1 (0.3)
AE leading to withdrawal from treatment	21 (7.4)	35 (12.1)	59 (20.3)	34 (11.6)
AE leading to dose modification/interruption	134 (47.5)	153 (52.9)	171 (59.0)	128 (43.8)

AE=adverse event; MTX=methotrexate; TCZ=tocilizumab.

The most frequent AEs were nausea, URTI, nasopharyngitis and hepatic transaminase increase. Infection risk remained a major safety issue with higher rates in patients on TCZ in combination with MTX. The serious infections included pneumonia, cellulitis and TB and there were 5 fatal

cases. Other serious risks were present and included anaphylaxis and hypersensitivity, malignancy, myocardial infarction and serious bleeding. There were no reported cases of GI perforation, opportunistic infection or demyelinating disorder in WA19926.

Laboratory parameter changes were consistent with previous studies and included increases in hepatic transaminases and lipids and decreases in neutrophils and platelets. Severe changes were not common and, apart from transaminases, were in line with pooled population data. There were no serious hepatic events in TCZ treated patients (there was one cases meeting Hy's Law definition in the placebo+MTX group). The early RA patients on TCZ, and in particular the combination of TCZ and MTX, were noted to be at a slightly higher risk of raised hepatic transaminases and premature study termination from this AE. The Sponsor's rationale was that this was due to more stringent safety withdrawal criteria in relation to raised ALT/AST.

The risk of anti-TCZ antibody formation in the early RA patients was low (1.1-2.2%) and did not appear associated with serious safety issues or loss of efficacy.

Overall, the safety profile of TCZ in the early RA, MTX-naïve population of WA19926 was consistent with known data. This group were found to have a slightly higher AE rate and death rate than that reported for pooled populations while the most notable difference was the higher risk of discontinuation due to AEs. When treated with TCZ monotherapy the safety profile of the early RA population appeared in line with that reported from the monotherapy population of other RA trials.

The data from WA19926 was in line with data from the submitted literature review however comparisons are difficult due to possibility of differing definitions of early RA and serious events.

The Sponsor has proposed two main changes to the Adverse Effects section of the PI. The first (below) covers the safety profile in the early RA population and is satisfactory.

> *Early Rheumatoid Arthritis*
>
> *Study VI (WA19926) evaluated 1162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the ACTEMRA treatment groups was consistent with the known safety profile of ACTEMRA (Table).*

The second change (below) covers the higher risk of hepatic transaminase elevation and the evaluator considers this addition adequate.

> *In Study VI, MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months) experienced more transient elevations in ALT > 3 x ULN compared with the all control population. This was observed in both ACTEMRA treated patients and MTX monotherapy patients.*

The longer term safety of TCZ in the early RA population still needs to be defined. As WA19926 was a 2 year study, the data to 104 weeks should be provided for evaluation as soon as available.

8.10.2. Long term safety in RA with inadequate MTX response

Study WA18695 was a long term extension study of WA17822 (a phase III 24 week placebo controlled study in moderate to severe RA) in which 538 patients were treated with 8 mg/kg TCZ every 4 weeks plus stable MTX. The total exposure was 2462 person years with a mean duration of 4.6 years. The retention rate for a 5 year study at 66% was acceptable. Long term treatment with 8 mg/kg TCZ in this trial did not reveal any new safety signals and the safety profile was in line with known data. The frequency of AEs did not increase with time and changes in laboratory parameters were relatively stable after initial changes in the first year of treatment. The withdrawal rate due to AEs was 4.2 per 100 PY.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of tocilizumab in the proposed usage are:

- Efficacy was demonstrated with TCZ 8 mg/kg in combination with MTX showing a superior response compared to MTX monotherapy on DAS28 remission rates after 6 months treatment.
- Efficacy for the 8 mg/kg plus MTX regimen was consistent across other parameters for disease remission including ACR and EULAR criteria.
- Efficacy of TCZ 8 mg/kg+MTX compared to MTX on reduction in joint damage (mTSS).
- Efficacy of TCZ 8 mg/kg monotherapy compared to MTX monotherapy was demonstrated for DAS28 remission but not for other parameters.
- A safety profile which was comparable to other adult RA population data.
- Long term data to 5 years in a moderate to severe RA population found no new safety signals.

9.2. First round assessment of risks

The risks of tocilizumab in the proposed usage are:

- Higher risk of hepatic transaminase elevation in the early RA population particularly with the 8mg/kg TCZ dose in combination with MTX. There were however no serious hepatic events in study WA19926.
- Higher risk of treatment withdrawal in the early RA population treated with TCZ particularly due to hepatic transaminase elevation.
- The known risks of infections, hypersensitivity reactions including anaphylaxis, GI perforation, serious bleeding, cardiac events and malignancy. There were no cases of demyelination reported. These risks were in line with data from previous studies in adults with RA.
- The risk of laboratory parameter changes including neutropenia, thrombocytopaenia and lipid elevation. These risks were in line with data from previous studies in adults with RA

9.3. First round assessment of benefit-risk balance

The efficacy tocilizumab in combination with MTX compared to MTX alone was demonstrated in patients with early RA who were MTX naïve. For the 8 mg/kg dose with MTX this was seen across all main efficacy parameters and for TCZ monotherapy the 8 mg/kg dose also was efficacious on DAS28 remission rates. In addition to response of disease remission, TCZ treatment with MTX in this early RA population was found to reduce the progression of joint damage after 52 weeks of treatment. The EMA (2003) guidelines state that “For agents which are claimed to prevent structural joint damage, it is currently recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons taken not less than one year apart ideally two years using full randomisation and pre-agreed criteria”. The more recent draft EMA guideline (2011) states that “measurement after 1 year may be sufficient to confirm efficacy in terms of endpoints relevant to slowing/prevention of structural damage claim. In exceptional cases a measurement after at least 6 months may be sufficient depending on the properties of the test drug; this has to be justified by robustness of the

method and convincing clinical data. It is important to demonstrate long-term maintenance of this effect for an additional 12 months."

Data from study WA17823 demonstrated inhibition of radiographic progression at 1 and 2 years in a population with inadequate response to MTX and the current approved indication for TCZ states that *ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate*. The evaluator agrees that in the early RA population there are consistent findings on joint damage for the combination of TCZ and MTX after 1 year treatment. Data from year two will be needed to demonstrate maintenance of this effect. By contrast, the lack of a significant inhibition of progression of joint damage in TCZ monotherapy group in WA19926 means that only the TCZ and MTX combination should be included in the indication in relation to efficacy on this endpoint.

The safety risks of the combination of TCZ and MTX were slightly higher than MTX alone in the early RA population although this was not an unexpected finding. The main difference was in adverse events leading to treatment withdrawal or dose modification/interruption. The safety in the early RA population compared to pooled population data from previous trials also found that in the earlier population the overall adverse event rate and death rate with TCZ treatment were slightly greater, however the SAE rate and rates of adverse events of special interest were generally in line with pooled data.

The notable difference in the early RA population was the higher rate of raised hepatic transaminases compared to patients who were inadequately responsive of DMARDs. In addition there was a higher rate of premature discontinuation due to AEs. The Sponsor proposes that this is due to the patients being MTX-naïve and also that there were differing protocol withdrawal criteria in relation to hepatic transaminase increase. Nonetheless these increased risks need to be defined and the proposed PI changes have captured this.

The safety database was adequate in size with nearly 800 patient years exposure. Overall, the safety profile in the early RA, MTX naïve population was in line with known data and no new safety signals were observed. The longer term safety of TCZ in the early RA population still needs to be defined and as WA19926 was a 2 year study, the data to 104 weeks should be provided for evaluation as soon as available.

Overall, the efficacy in early RA patients was demonstrated across a number of domains and was in the context of a safety profile in line with current data on RA patients. The increased risk of raised liver enzymes was generally transient, was not associated with serious hepatic events and has been covered in labelling. Therefore, the evaluator finds that the benefit-risk balance of tocilizumab given the proposed usage, is favourable subject to the changes recommended in Section 11 being adopted and the provision of long term safety data.

The long term data submitted in study WA18695 did not reveal new safety signals and so the current labelling remains adequate.

10. First round recommendation regarding authorisation

The evaluator recommends approval of the proposed changes to the product information for tocilizumab IV infusion for the following indication:

> *Rheumatoid Arthritis*
>
> *ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> ***in combination with methotrexate (MTX) in those not previously treated with MTX;***

The proposed change (below) to the indication in relation to monotherapy efficacy in joint damage reduction is not supported.

*ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given **alone or** in combination with methotrexate.*

These recommendations are subject to satisfactory responses to the comments on the PI and submission of the 2 year data from study WA19926.

[Details of recommended revisions to the PI other than to the *Indications* are not included in this CER extract]

11. Clinical questions

11.1. Pharmacokinetics

None

11.2. Pharmacodynamics

None

11.3. Efficacy

None

11.4. Safety

None

11.1. Product Information: Indication

Current wording [proposed addition underlined]:

*ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given **alone or** in combination with methotrexate.*

Comment: Data from study WA19926 found a numerical reduction in radiographic progression but not a statistically significant one when controlling for multiplicity was conducted in the hierarchical testing sequence. For this reason the evaluator cannot support using the finding in the indication and does not agree with the proposed change. The information has been included in the proposed new paragraph on MTX naïve, Early RA in the *Clinical Trial* section [of the PI].

12. Second round evaluation of clinical data submitted in response to questions

12.1. Product Information: Indication

The Sponsor agrees to remove the proposed claim and the draft PI has been revised accordingly as follows:

ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.

Evaluator's comment: This change is acceptable.

12.2. Study WA19926

The Sponsor, on request [see Section 10, above], also submitted the year 2 data (final CSR) from study WA19926 which was evaluated.

12.2.1. Methods

The included CSR reported data to the final week (104) of the study. The last patient last visit was conducted in July 2013.

Patients in the TCZ 4 mg/kg+MTX and placebo+MTX groups were switched to TCZ 8 mg/kg+MTX at week 52 if the DAS28 was >3.2 (termed "escape therapy") and continued on this to week 104. Patients in the TCZ 8mg/kg+MTX and TCZ 8mg/kg+placebo received the same treatment to week 104 (Figure 2 above, Study WA19926 Design). The study remained blinded to week 104 with only the statistical team being unblinded at week 52 for conducting the primary analysis.

Exploratory efficacy analyses were conducted on week 104 data. Missing data were handled using non-responder imputation for dichotomous endpoints and no imputation for continuous endpoints. This meant that the primary method for calculating DAS28 and ACR response rates used non-responder imputation for post-escape and withdrawal data. Radiological endpoints used primary imputation method of linear extrapolation for missing and post-escape data. Analysis was of the ITT population. Data on the TCZ 4mg/kg+MTX and placebo+MTX groups and patients who switched to TCZ 8 mg/kg+MTX at week 52 (escape) were analysed in their original treatment group for the duration of the study. For safety analyses patients were analysed according to treatment received.

12.2.2. Participant flow

Of the 1162 randomised patients, 1157 received study medication and 226 (78%), 237 (81%), 232 (80%) and 226 (78%) of the TCZ 8mg/kg+MTX, TCZ 8mg/kg+placebo, TCZ 4mg/kg+MTZ and placebo+MTX groups, respectively completed week 52. At Week 52, 95/290 (33%) patients in the TCZ 4mg/kg+MTX group and 142/289 (49%) patients in the placebo+MTX group were switched to escape therapy with TCZ 8 mg/kg+MTX. Patients with DAS28 ≤3.2 were maintained on the same treatment: 137 (47%) and 84 (29%) of the TCZ 4 mg/kg+MTX and placebo+MTX groups, respectively. All patients still in the TCZ 8 mg/kg+MTX (225/290 [78%]) and TCZ 8 mg/kg monotherapy (237/292 [81%]) groups continued on randomised treatment regardless of DAS28 score at week 52. The proportion of patient completing week 104 of the study was 70%, 71%, 68% and 70% of the TCZ 8mg/kg+MTX, TCZ 8mg/kg+placebo, TCZ 4mg/kg+MTZ and placebo+MTX groups, respectively.

There were 4 (2.8%) patients in the placebo+MTX escape group and 3 (3.2%) in the TCZ 4mg/kg+MTX escape group who should not have had treatment change due to their week 52 DAS28 score being ≤3.2.

In year 2 of the study, the rate of premature withdrawal for patients remaining on randomised treatment ("non-escape patients") was 7%, 10%, 9% and 3% of the TCZ 8mg/kg+MTX, TCZ 8mg/kg+placebo, TCZ 4mg/kg+MTZ and placebo+MTX groups, respectively. The rate of premature withdrawal in the escape patients (year 2) was higher at 19% and 15% of the TCZ 4mg/kg+MTX and placebo+MTX groups, respectively.

In year 2 there were 5 patients with major protocol violations, 4 took a prohibited medication and 1 took extra oral MTX.

12.2.3. Efficacy results

Results of key efficacy parameters are summarised in Table 8 and for the escape therapy population in Table 9.

Table 8: Overview of efficacy parameters (ITT Population)

Efficacy Parameter	Timepoint	Placebo +MTX (N=287)	TCZ 4 mg/kg +MTX (N=288)	TCZ 8 mg/kg +MTX (N=290)	TCZ 8 mg/kg +Placebo (N=292)
DAS28 Response Endpoints [No. (%) of Patients]					
DAS28 remission (DAS28 < 2.6) [a]	Wk 52	58 (20.2%)	104 (36.1%)	143 (49.3%)	118 (40.4%)
	Wk 104	46 (16.0%)	81 (28.1%)	138 (47.6%)	127 (43.5%)
LDA (DAS28 ≤ 3.2) [a]	Wk 52	86 (30.0%)	137 (47.6%)	168 (57.9%)	147 (50.3%)
	Wk 104	61 (21.3%)	99 (34.4%)	161 (55.5%)	150 (51.4%)
ACR Response Endpoints [No. (%) of Patients]					
ACR20 [a]	Wk 52	168 (58.5%)	188 (65.3%)	197 (67.9%)	191 (65.4%)
	Wk 104	73 (25.4%)	114 (39.6%)	189 (65.2%)	180 (61.6%)
ACR50 [a]	Wk 52	119 (41.5%)	158 (54.9%)	163 (56.2%)	148 (50.7%)
	Wk 104	63 (22.0%)	105 (36.5%)	167 (57.6%)	155 (53.1%)
ACR70 [a]	Wk 52	84 (29.3%)	109 (37.8%)	126 (43.4%)	108 (37.0%)
	Wk 104	50 (17.4%)	91 (31.6%)	135 (46.6%)	115 (39.4%)
Radiographic Endpoints [Mean (SD)]					
Mean (SD) change from baseline in:					
mTSS [b]	Wk 52	0.97 (3.207)	0.75 (5.901)	0.13 (1.278)	0.30 (2.699)
	Wk 104	1.88 (6.242)	1.43 (11.669)	0.19 (2.081)	0.62 (4.756)
Erosion score [b]	Wk 52	0.52 (2.075)	0.30 (2.061)	0.09 (0.878)	0.08 (1.318)
	Wk 104	1.01 (4.040)	0.57 (4.062)	0.11 (1.341)	0.19 (1.974)
JSN score [b]	Wk 52	0.45 (1.697)	0.45 (4.024)	0.04 (0.705)	0.22 (2.120)
	Wk 104	0.87 (3.284)	0.86 (7.958)	0.08 (1.175)	0.43 (3.981)
Mean (SD) APR for mTSS [c]	BL to Wk 52	0.87 (2.706)	0.33 (1.618)	0.09 (0.894)	0.14 (1.370)
	Wk 52 to 104	0.23 (0.762)	0.12 (0.813)	0.00 (0.621)	0.13 (0.776)
HAQ-DI					
No (%) patients with HAQ-DI ≥ 0.3 response [d]	n	80	120	205	208
	Wk 104	64 (80.0%)	103 (85.8%)	171 (83.4%)	171 (82.2%)
Mean (SD) change from baseline [d]	Wk 104	-1.01 (0.760)	-1.20 (0.782)	-1.02 (0.706)	-0.98 (0.747)

APR=annualized progression rate; BL=baseline; LDA=low disease activity; mTSS= modified Total Sharp-van de Heijde Score; JSN=modified Joint Space Narrowing score; Wk=week.

a Patients who received escape therapy, withdrew prematurely or where a DAS28/ACR could not be calculated, were set to 'non-responder'.

b Missing data were imputed using linear extrapolation.

c Observed data.

d No imputation for missing data.

Table 9: Overview of key efficacy parameters after 52 weeks of escape therapy (ITT Population, Escape Patients)

Efficacy Parameter	Timepoint	Placebo +MTX Post-Escape N=142	TCZ 4 mg/kg +MTX Post-Escape N=95
DAS28 Response Endpoints [No. (%) of Patients] [a]			
DAS28 remission (DAS28 <2.6)	Wk 52	73 (51.4%)	29 (30.5%)
LDA (DAS28 ≤3.2)	Wk 52	92 (64.8%)	41 (43.2%)
ACR Response Endpoints [No. (%) of Patients] [a]			
ACR20	Wk 52	61 (43.0%)	28 (29.5%)
ACR50	Wk 52	43 (30.3%)	16 (16.8%)
ACR70	Wk 52	23 (16.2%)	6 (6.3%)
Radiographic Endpoints [Mean (SD)] [b]			
Change from baseline in mTSS [c]	Wk 52	1.49 (3.952)	0.68 (2.703)
	Wk 104	1.57 (4.557)	0.56 (2.627)
Annualized Progression Rate for mTSS	BL to Wk 52	1.43 (3.811)	0.65 (2.555)
	Wk 52 to 104	0.10 (1.156)	0.01 (0.692)
HAQ-DI [Mean (SD)] [a]			
Change from baseline in HAQ-DI	Wk 52	-0.25 (0.481)	0.01 (0.380)

BL=baseline; LDA=low disease activity; mTSS=modified Total Sharp-van de Heijde Score.
a Based on post-escape baseline.
b Based on original baseline.
c Based on observed data (no imputation for missing data) with post-withdrawal data included.

The DAS28 remission rate was maintained from week 52 to 104 in the TCZ 8 mg/kg+MTX group (49.3% to 47.6%) and also in the TCZ 8mg/kg+placebo (40.4% to 43.5%). While 75-78% of patients in these groups remained in DAS28 remission there were 22-25% of patients with DAS28 remission at week 52 who shifted to being a non-responder by week 104. There was also a similar rate of patients with slow treatment response who shifted from non-response at week 52 to response at week 104.

The rate of low disease activity (DAS28 ≤3.2) was maintained from week 52 to week 104 in both TCZ 8mg groups. In the TCZ 4mg/kg+MTX and placebo +MTX groups there was a decline in the rate of low disease activity while for those switching to escape therapy there was some improvement.

The mean DAS28 score was maintained from week 52 to 104 in the TCZ 8 mg group and reduced in the TCZ 4mg/kg+MTX and placebo +MTX groups presumably due to the inclusion of data from patients switching therapy. The DAS28 component scores (mean values for SJC28, TJC28, ESR and patient's global assessment of disease activity) were maintained to week 104 in the TCZ 8 mg groups.

For the escape therapy patients the proportion achieving DAS28 remission at week 104 was 30.4% and 51.4% in the TCZ 4mg/kg+MTX and placebo +MTX groups, respectively indicating a greater response in those switching from MTX monotherapy and a comparable response in this group to those on TCZ 8mg for 104 weeks.

In the TCZ 8 mg groups the ACR20/50/70 response rates were maintained from week 52 to 104 and most patients (82-85%) who were responders on ACR50 at week 52 remained so at week 104. A major clinical response (ACR70 response for 24 weeks or longer) was achieved in 34-48% of the TCZ groups compared to 22% of the placebo+MTX group. The ACR core set components were maintained to week 104 but did not show further improvement after week 52 in the TCZ 8 mg groups.

Mean CDAI scores were maintained in all treatment groups. Post-hoc exploratory analyses of Boolean and Index remission rates using non-responder imputation for post-escape and withdrawal data showed response maintenance in the TCZ 4mg/kg+MTX and placebo +MTX groups and small increases to week 104 in the TCZ 8mg groups.

Post-hoc analyses of the escape therapy patients showed some improvement on ACR endpoints on changing to TCZ 8 mg/kg+MTX. These results on the ACR core set parameters were similar to the TCZ 8mg/kg+MTX group.

Radiographic endpoints: Baseline and week 104 radiographs were available in 73-76% of patients in each group. The mean change from baseline in the mTSS was 0.13 at week 52 and 0.19 at week 104 in the TCZ 8mg/kg+MTX group and was higher, although it was a small increase, in the TCZ 8mg/kg+placebo group (0.3 at week 52 and 0.62 at week 104). There was greater progression from week 52 to 104 in the TCZ 4mg/kg+MTX group (0.75 and 1.43) and the placebo+MTX group (0.97 and 1.88).

> **Comment:** For primary analysis, patients with a missing week 104 X-ray, or who were on escape therapy from week 52, had the week 104 result imputated. Consequently, the proportion with imputated values was high (24%, 26%, 51% and 65% in the TCZ 8mg/kg+MTX, TCZ 8mg/kg+placebo, TCZ 4mg/kg+MTZ and placebo+MTX groups, respectively) particularly in the latter two groups.

The mean change from baseline in the modified Sharp Erosion and Joint Space Narrowing scores were maintained from week 52 to 104 in the TCZ 8 mg/kg+MTX group, showed small increase in the TCZ 8mg/kg+placebo and TCZ 4mg/kg+placebo groups and greater increases in the MTX+placebo group. The proportion of patients with no radiographic progression on mTSS at week 104 was 83%, 80%, 73% and 68% of the TCZ 8mg/kg+MTX, TCZ 8mg/kg+placebo, TCZ 4mg/kg+MTZ and placebo+MTX groups, respectively.

For patients on escape therapy, the mean change from baseline in the mTSS changed little from week 52 to 104 indicating little further joint damage.

HAQ-DI. The mean HAQ-DI reduced in the first year and was maintained at this level in the second treatment year in the TCZ 8mg/kg+MTX group. An improvement was seen in the TCZ 4mg/kg +MTX and placebo +MTX groups in year 2.

> **Comment**: There was no imputation for missing data on this analysis and the Sponsor proposes that finding this was due to enrichment of the cohort with responders as there was the loss of non-responders to the escape therapy. The evaluator agrees with this proposition.

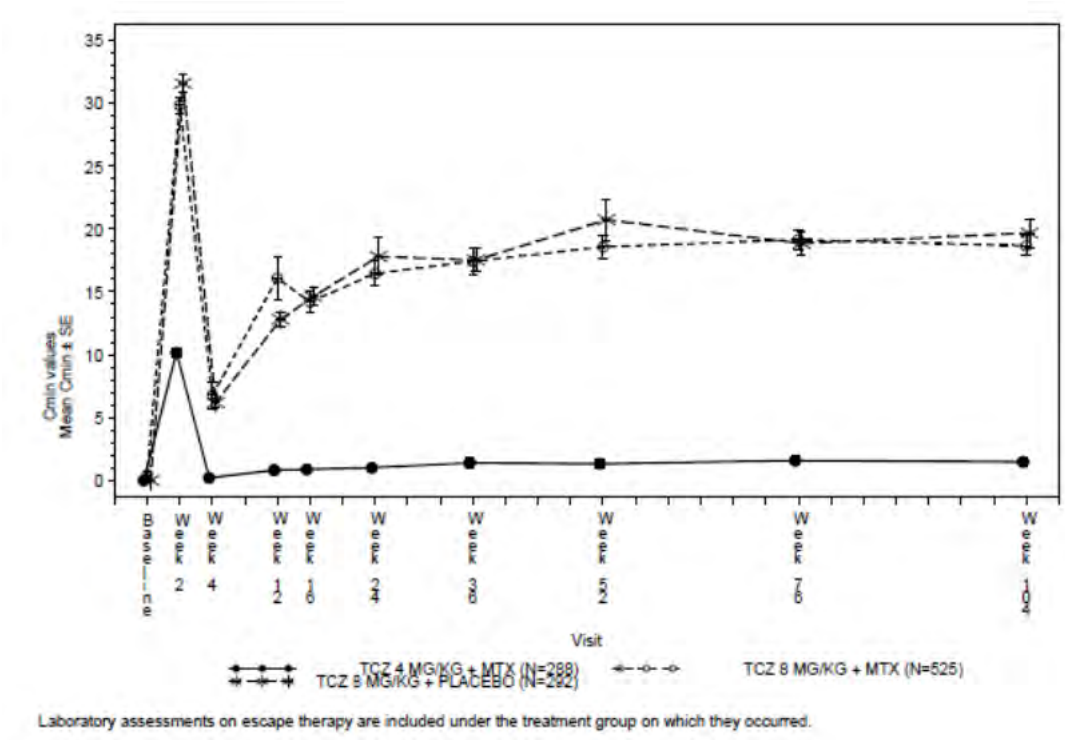
Escape therapy patients showed little change in mean HAQ-DI during year 2 (mean change from week 52 baseline of -0.25 and 0.01 in the placebo+MTX and TCZ 4m/kg+MTX groups, respectively).

A maintenance of response on the FACIT-Fatigue Score, SF-36 Physical Component Score and SF-36 Mental Component Score was seen in the TCZ 8mg/kg groups from week 52 to 104 although there was no imputation for missing data.

12.2.4. Pharmacodynamics and Pharmacokinetics

During year 2, data on pre-dose concentrations of IL-6, sIL-6R and TCZ were in line with findings from the first treatment year (Figure 7).

Figure 7: Plot of mean (± SE) Cmin TCZ concentration up to Week 104 (µg/mL) (PK evaluable population)



Comment: Due to the inclusion of escape therapy patients in the TCZ 8mg/kg+MTX group from week 52 there are different sample sizes at various visits and results can only be viewed as indicative.

12.2.5. Safety results

12.2.5.1. Exposure

The mean exposure duration to IV treatment in the TCZ 8mg/kg+MTX group was 1.29 years and total patient years exposure was 682 years which was longer than the other groups (332 to 481 years) due to the inclusion of escape therapy patients. The mean weekly MTX dose was lower in the TCZ 8mg/kg+MTX group compared to the other groups (14.57 mg vs 15.40 to 16.76 mg).

12.2.5.2. Adverse events

The rates of AEs per 100 patient years were similar between TCZ and placebo+MTX groups (336.6-391.5 vs. 367.9 AEs per 100 PY, respectively). Adverse events followed a similar profile to that reported in the first treatment year. There was a higher rate of AEs in the Investigations SOC in the TCZ 8mg/kg+MTX group compared to the placebo+MTX group (51.4 vs 33.0 AEs per 100 PY) primarily due to increased transaminases. The rate of severe AEs was highest in the TCZ 4mg/kg+MTX group (17.2 per 100 PY) compared to the other groups (9.4-11.7). Analysis of the rates of AEs by 6 month periods showed highest rates in the first 6 months and did not reveal any increase in rates over time.

12.2.5.3. AEs of special interest

Table 10 summarises AEs of special interest. There was a higher rate of serious infections in the TCZ groups and opportunistic infections only occurred in the TCZ 8mg/kg groups. Three opportunistic infections occurred in year 2 (disseminated histoplasmosis, B. pseudomallei pneumonia and oesophageal candidiasis). There was one case of tuberculosis in year 2 in an escape therapy patient. Serious hypersensitivity, anaphylactic reactions and serious MIs also only occurred in the TCZ groups. Of the five serious hypersensitivity cases, none occurred in year 2 and the two anaphylaxis cases occurred in the first year of treatment. There were no

serious demyelinating disorders or serious hepatic AEs reported. There were eight malignancies reported in year 2 (BCC, small cell lung cancer, two endometrial cancers, two SCC, prostate cancer, and metastatic cancer with undetermined primary) all of which were in TCZ-treated patients.

Table 10: Overview of Adverse Events of Special Interest: Rates [95% CI] per 100 patient-years (Safety Population)

	Placebo +MTX N=282	TCZ 4 mg/kg +MTX N=289	TCZ 8 mg/kg +MTX N=527	TCZ 8 mg/kg +Placebo N=292
PY Exposure	339.53	394.64	718.39	502.26
Infections and infestations (Section 7.9.1)				
No. events	333	447	642	474
Rate per 100 PY [95% CI]	98.1 [87.8, 109.2]	113.3 [103.0, 124.3]	89.4 [82.6, 96.6]	94.4 [86.1, 103.3]
Serious infections (Section 7.9.1.2)				
No. events	6	16	25	20
Rate per 100 PY [95% CI]	1.8 [0.6, 3.8]	4.1 [2.3, 6.6]	3.5 [2.3, 5.1]	4.0 [2.4, 6.1]
Opportunistic infections (Section 7.9.1.4)				
No. events	0	0	2	1
Rate per 100 PY [95% CI]	0.0 [0.0, 1.1]	0.0 [0.0, 0.9]	0.3 [0.0, 1.0]	0.2 [0.0, 1.1]
Hypersensitivity AE (Section 7.9.2) [a]				
No. events	66	105	113	80
Rate per 100 PY [95% CI]	19.4 [15.0, 24.7]	26.6 [21.8, 32.2]	15.7 [13.0, 18.9]	15.9 [12.6, 19.8]
Serious anaphylaxis AEs (Section 7.9.3)				
No. events	0	1	0	1
Rate per 100 PY [95% CI]	0.0 [0.0, 1.1]	0.3 [0.0, 1.4]	0.0 [0.0, 0.5]	0.2 [0.0, 1.1]
Serious malignancy AEs (Section 7.9.4)				
No. events	3	4	3	5
Rate per 100 PY [95% CI]	0.9 [0.2, 2.6]	1.0 [0.3, 2.6]	0.4 [0.1, 1.2]	1.0 [0.3, 2.3]
Serious bleeding AEs (Section 7.9.5)				
No. events	2	3	4	2
Rate per 100 PY [95% CI]	0.6 [0.1, 2.1]	0.8 [0.2, 2.2]	0.6 [0.2, 1.4]	0.4 [0.0, 1.4]
Serious stroke AEs (Section 7.9.6)				
No. events	2	3	3	1
Rate per 100 PY [95% CI]	0.6 [0.1, 2.1]	0.8 [0.2, 2.2]	0.4 [0.1, 1.2]	0.2 [0.0, 1.1]
Serious myocardial infarction AEs (Section 7.9.7)				
No. events	0	3	2	1
Rate per 100 PY [95% CI]	-	0.8 [0.2, 2.2]	0.3 [0.0, 1.0]	0.2 [0.0, 1.1]
Serious GI perforations (Section 7.9.8)				
No. events	1	0	0	1
Rate per 100 PY [95% CI]	0.3 [0.0, 1.6]	0.0 [0.0, 0.9]	0.0 [0.0, 0.5]	0.2 [0.0, 1.1]
Serious hepatic AEs				
No. events	0	0	0	0
Serious demyelinating AEs				
No. events	0	0	0	0

a Hypersensitivity event defined as any AE that occurred during or within 24 hours of a TCZ/placebo infusion and not deemed 'unrelated' to trial treatment. Includes all types of AE that occurred within 24 hours of study drug administration, regardless of whether or not they were clinically consistent with hypersensitivity.

12.2.5.4. Deaths

There were 14 deaths reported in the study of which five occurred in year 2. The rate was highest in the TCZ 4mg/kg+MTX group compared to the other groups (1.27 vs 0.56-0.60). The deaths, all in TCZ groups, were duodenal ulcer and haemorrhage, interstitial lung disease, endometrial cancer, congestive heart failure and metastatic cancer with undetermined primary.

12.2.5.5. SAEs

The rate of SAEs was higher in TCZ groups than the placebo+MTX group (11.6-14.7 vs. 9.1 SAEs per 100 PY). The most frequent SAEs were infections.

12.2.5.6. Discontinuations due to AEs

The rate of AEs leading to withdrawal was higher in the TCZ groups than in the placebo+MTX group (9.9-12.0 vs. 6.5 AEs per 100 PY). Dose modifications and interruptions due to AEs were more common in the TCZ+MTX groups than in the placebo+MTX or TCZ 8 mg/kg+placebo groups.

12.2.5.7. Pregnancies

Of the 10 reported pregnancies, three were in year 2. These three were in patients treated with TCZ and all resulted in spontaneous abortion.

12.2.5.8. Laboratory data

Mean platelet and mean neutrophil counts remained steady from week 52 to 104. Only one of the five grade ≥3 decrease in platelets occurred during the second treatment year. Of the 40 grade ≥3 decrease in neutrophils, 18 occurred in the second year. Serum chemistry showed changes in liver function and lipid parameters. Mean ALT, AST and total bilirubin levels were steady during week 52 to 104. There were no cases of altered liver function meeting Hy's Law criteria. There was an increase in mean fasting cholesterol, TG, LDL and HDL which was greater in the TCZ groups, occurred early in treatment and appeared to remain relatively stable over year 2. Clinically relevant shifts were more frequent with the 8mg/kg TCZ dose.

12.2.5.9. Vital signs

Vital signs showed no remarkable findings apart from a small mean increase in body weight across all groups which was highest in the placebo+MTX group (5.1 vs 2.9-3.9 kg).

12.2.5.10. Safety in escape patients

On switching to escape therapy there was no increase in AE rates in either the TCZ 4 mg/kg+MTX of placebo+MTX group. The AE profile in these patients was similar to that reported for other TCZ groups. The rate of SAEs did increase on escape therapy particularly in the placebo+MTX group from 7.0 to 10.9 SAEs per 100 PY. As to be expected the most common AE leading to discontinuation in escape therapy patients was increased transaminases. Changes in laboratory parameters were also consistent with known effects of TCZ 8mg/kg treatment.

12.2.5.11. Immunogenicity

In the TCZ groups, the rate of developing TCZ antibodies was 4/290 (1.4%) in the TCZ 8 mg/kg+MTX group, 3/292 (1.0%) in the TCZ 8 mg/kg+placebo group and 10/288 (3.5%) in the TCZ 4 mg/kg+MTX group. The rate of antibodies in the placebo+MTX group was 3.5%. None of the 9 subjects with neutralising anti-TCZ antibodies was withdrawn for lack of treatment efficacy.

There were 19 patients (excluding escape therapy patients) with a clinically significant hypersensitivity event. All received TCZ. Two were anti-TCZ antibody positive and one patient in the TCZ 8mg/kg+placebo group had a positive IgE assay and was withdrawn due to a hypersensitivity event of urticaria.

One (1.1%) of 95 TCZ 4mg/kg+MTX escape therapy treated patients became anti-TCZ positive while none of the placebo+MTX escape therapy group developed antibodies.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After review of data submitted following the first round of evaluation, the benefits of tocilizumab in the proposed usage, in addition to those listed in Section 9.1 now also include:

- Efficacy of TCZ 8mg/kg+MTX appears to be maintained after 2 years of treatment. This was consistent across measured parameters. There was, however, no evidence of further improvement in efficacy with longer treatment duration.
- Radiographic data indicated a maintained reduction in joint damage (mTSS) when treated with TCZ 8 mg/kg+MTX.
- No new safety signals were evident in this early RA population when treated with TCZ for two years.

13.2. Second round assessment of risks

After review of data submitted following the first round of evaluation, the risks of tocilizumab remain unchanged from that listed in Section 9.2.

13.3. Second round assessment of benefit-risk balance

In patients with early moderate to severe RA who are MTX-naïve, the data from the final study report of WA19926 indicated that the efficacy achieved after one year of treatment with tocilizumab was maintained during the second treatment year. While the analysis was exploratory and there was no formal statistical testing, the data were consistent across efficacy endpoints of DAS28, ACR 20/50/70 and HAQ-DI. Consistent with data after year one of treatment, the efficacy remained greatest with the TCZ 8mg/kg+MTX treatment regimen. There was, however, no further improvement in efficacy with ongoing treatment.

The impact on joint damage that was noted in year one was found to be maintained during year two. Radiographic data showed that the mean change from baseline in mTSS score remained steady in the second year of treatment in the TCZ 8mg/kg+MTX group. The effect was less notable in the TCZ 8mg/kg monotherapy group and, due to the lack of statistically significant result in year one in this group, no formal conclusions can be drawn on the TCZ monotherapy regimen.

Data on the TCZ 4mg/kg+MTX and placebo+MTX groups are difficult to interpret due to the study design and use of the so-called escape therapy of TCZ 8mg/kg+MTX in non-responders. For example the high number of subjects with imputated values on radiographic data in these groups (51% of the TCZ 4mg/kg+MTX group) makes interpretation of results difficult.

The safety database included 682 patient years of treatment with TCZ 8mg/kg+MTX. There were no new safety signals identified and the profile of events was consistent with data from the first treatment year. The rate of AEs was higher with the lower TCZ dose (4mg/kg+MTX) and there is no clear explanation for this. Laboratory parameter changes remained relatively stable over the second year of treatment. When analysed in 6 monthly intervals, there was also no evidence for an increase in AE rates over time. The highest rates remain in the first 6 months of treatment, nonetheless, the risks of tocilizumab are ever present after two years of treatment.

Safety in patients switching to TCZ 8mg/kg+MTX was in line with what would be expected from this higher dose combination and it appears that switching treatment was tolerated.

Overall, in the early RA population after two years treatment, efficacy of tocilizumab with methotrexate was maintained and the safety risks were stable indicating little change in the benefit-risk balance for tocilizumab from that discussed after the first round assessment. The Sponsor has also satisfactorily addressed the requested changes to the PI.

14. Second round recommendation regarding authorisation

After the second round of evaluation, the evaluator recommends approval of the proposed changes to the product information for tocilizumab IV infusion for the following indication:

> *Rheumatoid Arthritis*
>
> *ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> ***in combination with methotrexate (MTX) in those not previously treated with MTX;***

The Sponsor has withdrawn the proposed change to the indication in relation to monotherapy efficacy in joint damage reduction.

15. References

EMA 2003. Points to consider on the clinical investigation of medicinal products other than NSAIDS for treatment of rheumatoid arthritis". CPMP/EWP/556/95 rev1/Final. London 2003.

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