24 July 2014
EMA/552413/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RoActemra

International non-proprietary name: TOCILIZUMAB

Procedure No. EMEA/H/C/000955/II/0032

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Background information on the procedure 4
1.1. Type II variation 4
1.2. Steps taken for the assessment of the product 4
2. Scientific discussion 5
2.1. Introduction 5
2.2. Non-clinical aspects 6
2.3. Clinical aspects 7
2.3.1. Introduction 7
2.3.2. Pharmacokinetics 7
2.3.3. Pharmacodynamics 19
2.3.4. Discussion on clinical pharmacology 25
2.3.5. Conclusions on clinical pharmacology 30
2.4. Clinical efficacy 30
2.4.1. Main study 30
2.4.2. Discussion on clinical efficacy 57
2.4.3. Conclusions on the clinical efficacy 60
2.5. Clinical safety 60
2.5.1. Discussion on clinical safety 73
2.5.2. Conclusions on clinical safety 75
2.5.3. PSUR cycle 75
2.6. Risk management plan 75
2.7. Update of the Product information 112
3. Benefit-Risk Balance 113
4. Recommendations 115

List of abbreviations

Abs	antibodies
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-CCP Ab	Anti-citrullinated protein antibody
AST	aspartate aminotransferase
ATP	Adult Treatment Panel
AUC	area under the time-concentration curve
CDAI	clinical disease activity index
CI	confidence interval
C_{max}	maximum observed plasma concentration immediately at the end of the infusion
C_{min}	minimum observed (pre-dose) plasma concentration
CRP	C-reactive protein
C_{wk2}	serum concentration at Day 14 after dosing in Week 2
DAS28	Disease Activity Score of 28 joints
DMARD	disease modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire disability index
HDL	high-density lipoprotein
IL-6 sR	interleukin-6 soluble receptor
IL-6	interleukin-6
IV	intravenous
JSN	joint space narrowing
LDL	low-density lipoprotein
LTE	long-term extension
MAH	marketing authorisation holder
MCR	major clinical response
MI	myocardial infarction
mTSS	modified total Sharp score
MTX	methotrexate
NSAIDs	non-steroidal anti-inflammatory drugs
PD	pharmacodynamic(s)
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PSUR	periodic safety update report
PY	patient-years
RA	rheumatoid arthritis
SD	standard deviation
SJC	swollen joint count
SmPC	summary of product characteristics
TB	tuberculosis
TCZ	tocilizumab
TJC	tender joint count
TNF-α	tumour necrosis factor alpha
ULN	upper limit of normal
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd. submitted to the European Medicines Agency on 4 June 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Roactemra	tocilizumab	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

The MAH applied for an update of sections 4.1 and 5.1 of the SmPC and consequential changes to section 1 of the Package Leaflet in order to extend the indication to the treatment in combination with methotrexate (MTX) of severe, active and progressive RA in adults not previously treated with MTX. In addition the MAH took the opportunity to align the PI with version 9 of the QRD template and to correct some typographical errors throughout the PI.

The variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0185/201 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0179/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

CHMP Rapporteur: Jan Mueller-Berghaus CHMP Co-Rapporteur: Agnes Gyurasics

PRAC Rapporteur: Brigitte Keller-Stanislawski

Submission date:	4 June 2013
Start of procedure:	23 August 2013
Rapporteur's preliminary assessment report circulated on:	15 October 2013
CoRapporteur's preliminary assessment report circulated on:	15 October 2013
PRAC Rapporteur Assessment Report circulated on:	21 October 2013
PRAC Meeting, adoption of PRAC Advice	7 November 2013
Joint Rapporteur's updated assessment report circulated on:	18 November 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 November 2013
MAH's responses submitted to the CHMP on:	February 2013
Joint Rapporteur's assessment report on the MAH's responses circulated on:	28 March 2014
PRAC Rapporteur Assessment Report circulated on:	24 March 2013
PRAC RMP advice and assessment overview adopted by PRAC	10 April 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2014
MAH's responses submitted to the CHMP on:	May 2014
Rapporteur's assessment report on the MAH's responses circulated on:	24 June 2014
PRAC Rapporteur Assessment Report circulated on:	24 June 2014
CHMP opinion:	24 July 2014

2. Scientific discussion

2.1. Introduction

About the disease

Rheumatoid arthritis (RA) is a progressive, systemic autoimmune disease characterised by synovitis that damages diarthroidal joints and is accompanied by fatigue, anaemia, and osteopenia. RA has a prevalence of 0.5% to 1.0% and a peak incidence between 40 and 60 years of age and affects primarily women.

Non-steroidal anti-inflammatory drugs (NSAIDs) provide only symptomatic relief. Disease-modifying anti-rheumatic drugs (DMARDs) maintain or improve physical function and retard radiographic joint damage. More recently, biologic compounds that target tumour necrosis factor alpha (TNF-α), B cells, or T cells have been used successfully to treat RA, but approximately 30% to 40% of patients fail to respond to these therapies.

It is now accepted that there is a 'window of opportunity' within the early stages of RA during which there is a therapeutic opportunity to maximize disease retardation in terms of controlling symptoms, limiting joint damage, and improving physical function (Sesin & Bingham 2005; Cush 2007). Disease remission for patients with early RA and low disease activity for patients with long disease duration, are today's accepted treatment goals.

About the product

Tocilizumab (RoActemra, TCZ) is a recombinant, humanized 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 pleiotropic, pro-inflammatory, multifunctional cytokine produced by a variety of cell types, and it has been implicated in the pathogenesis of several inflammatory and autoimmune disorders, including RA. Elevated IL-6 levels have been observed in the serum and synovial fluid of RA patients, and levels correlate with disease activity.

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

The recommended posology for adult RA in the EU is 8 mg/kg body weight, given as an intravenous (IV) infusion once every four weeks.

The development program/Compliance with CHMP Guidance/Scientific Advice

The CHMP Scientific Advice was not obtained prior to the initiation of study WA19924.

GCP

The WA19926 study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines or with the laws of the country if these afforded greater protection of subjects, as declared by the MAH.

Type of application and other comments on the submitted dossier

This Type II variation is to extend the adult indication for RoActemra to include the following: the treatment of severe, active and progressive RA in adults not previously treated with MTX. In addition, the MAH proposed to amend the indication statement regarding the joint damage to the following: RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given alone or in combination with methotrexate.

This variation application is based on the results of the Week-52 analysis of the pivotal Phase III trial, WA19926 (FUNCTION). Supporting data is provided from previous phase III studies and from long term extension studies.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Table 1. Tabular overview of key clinical studies of tocilizumab in patients with RA

Study Number (Name)	Design	Patient Population; No. of Patients	Treatment Regimen	Primary Endpoint	Status and Key Outcome
Pivotal Study in Early RA					
WA19926 (FUNCTION) Phase III Study	Phase III, multicenter, randomized, double-blind, parallel group 104-wk study	MTX-naïve with moderate to severe active RA ≤ 2 years duration with progressive disease enrolled: n=1162	TCZ 4 or 8 mg/kg IV q4w in combination with MTX, TCZ 8 mg/kg monotherapy or MTX alone for 104 weeks	DAS28 remission at Week 24	Ongoing. The study met its primary endpoint.
Studies of TCZ in Combination with MTX or DMARDS					
WA17822 (OPTION)	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group	MTX-IR with moderate to severe active RA enrolled: n=623	TCZ 4 or 8 mg/kg IV q4w in combination with MTX versus MTX alone for 24 weeks.	ACR20 at Week 24	Completed. The study met its primary endpoint.
WA18063 (TOWARD)	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group	DMARD-IR with moderate to severe active RA enrolled: n=1220	TCZ 8 mg/kg IV q4w in combination with background DMARD versus DMARD alone	ACR20 at Week 24	Completed. The study met its primary endpoint.
WA18062 (RADIATE)	Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group	TNF-IR or TNF intolerant with moderate to severe active RA enrolled: n=499	Anti-TNF agent discontinued prior to randomization TCZ 4 or 8 mg/kg IV q4w in combination with MTX versus MTX alone for 24 weeks.	ACR20 at Week 24	Completed. The study met its primary endpoint
WA17823 (LITHE)	Phase III multicenter, randomized, double-blind, placebo controlled, parallel-group	MTX-IR with moderate to severe active RA enrolled: n=1196	TCZ therapy 4 or 8 mg/kg IV q4w in combination with MTX versus MTX alone.	ACR20 at Week 24; change in Genant mTSS, AUC of HAQ-DI at Weeks 52 and 104	Completed The study met its primary endpoint.

Study Number (Name)	**Design**	**Patient Population; No. of Patients**	**Treatment Regimen**	**Endpoints**	**Status and Key Outcome**
Studies of TCZ as Monotherapy					
WA17824 (AMBITION)	Phase III, randomized, double-blind, double-dummy, parallel-group	MTX-naïve or discontinued MTX with moderate to severe RA, with mean DAS28 of 6.7 at baseline; enrolled: n = 673	8 mg/kg of TCZ q4w plus oral placebo vs. IV MTX plus placebo for 24 weeks	ACR20 at Week 24	Completed. The study met its primary endpoint
MRA012JP (SAMURAI)	Phase III, multicenter, randomized, controlled, X-ray reader–blinded	DMARD-IR with moderate or severe RA <5 yrs duration,, with baseline DAS28 of 6.5; enrolled: n = 306	Conventional DMARD vs. 8 mg/kg of TCZ q4w for 52 weeks	Change in van der Heide Erosion Score at Week 52	Completed. TCZ was superior to DMARD.

ACR = American College of Rheumatology; DAS28 = Disease Activity Score 28; DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; IR = inadequate responder; IV = intravenous; mTSS: modified total Sharp score, MTX = methotrexate; po = by mouth; q1w = once weekly; q2w = every 2 weeks; q4w = every 4 weeks; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumor necrosis factor; TCZ = tocilizumab.

2.3.2. Pharmacokinetics

No separate PK/PD study was conducted. PK/PD and immunogenicity parameters were measured in the pivotal study and summarized descriptively. Given the reduced set of PK data available from the pivotal study, which did not allow analysis of detailed aspects of the PK, in the Assessment focus is given on the PK in the target population. The derived PK data were compared with historical data.

No changes to the SmPC section 5.2 (Pharmakokinetic properties) were proposed with this variation application. Thus the submitted information was intended to support the assumption of a comparable PK profile for MTX naïve RA patients and the previously approved indication of RA patients.

Analytical methods

Pivotal study WA19926 (FUNCTION): The bioanalytical reports for TCZ concentration, IL-6 concentration, sIL-6R concentration, and screening as well as confirmed positive anti-TCZ antibody assay were provided.

The concentrations of interleukin-6 soluble receptor (IL-6 sR) were determined in human serum according to a validated quantitative solid phase sandwich ELISA designed to measure IL-6 sR in cell culture supernatant, serum, plasma and urine. The concentrations of IL-6 sR were determined successfully in a total of 3728 out of 3755 human serum samples obtained from clinical study WA19926. The study was not GLP conform. The lower limit of quantification was 12.5 ng/mL in native serum. The calibration range was 0.0313 – 2.00 ng/mL (concentrations in assay), equivalent to 12.5 – 800 ng/mL in native serum. Aliquots of 10.0 µL of serum were used. The precision of the assay as ranged from 8.5% to 9.2%. The accuracy of the assay was between 99.7% and 102.2%.

The concentrations of neutralizing anti-TCZ antibodies were determined in human serum according to the validated ELISA method in a total of 121 human serum samples obtained from clinical study WA19926. Anti-TCZ antibodies were analysed using aliquots of 40.0 µL of serum. The quality of determinations was satisfactory throughout the study. The lower limit of quantification for anti-TCZ antibodies was 211 ng-eq./mL (concentration in serum) with an analytical range of 21.1 – 240 ng-eq./mL (concentrations in assay), equivalent to 211 – 2400 ng-eq./mL in native serum. The precision of the assay as determined from the analysis of quality control samples ranged from 8.2% to 14.4%. The accuracy of the assay was between 91.4% and 101.4%.

Test samples for anti-TCZ antibodies were analysed initially using a validated bridging ELISA method (Screening assay). In serum samples found positive in the Screening Assay, the presence of specific anti-TCZ antibodies was confirmed or excluded using the same ELISA method with an appropriate immunodepletion step (addition of excess Tocilizumab). Samples were confirmed as containing specific anti-Tocilizumab antibodies if the mean assay response of the matching control sample was above the plate specific cut point and the mean assay response of the confirmation sample was less than 80% of the control sample or in case the response of the aliquot measured with excess TCZ dropped below the plate-specific cut point. A total of 2416 human serum samples obtained from clinical study WA19926 were screened for the presence of anti-Tocilizumab antibodies. For 2413 samples valid results were obtained for the anti-TCZ antibody screening assay. For one sample (subject 13200, sample 104) the initial results was invalid and the remaining volume was insufficient for analysis. Therefore, for this sample NOR was reported. For two samples (subject 16450, sample 104 and subject 12137, sample 174) insufficient volume for analysis was provided and for these samples NOS were reported. In this study 325 out of 2416 human serum samples screened for the presence of anti-Tocilizumab antibodies were positive in the screening assay. 118 samples were confirmed positive for the presence of anti-Tocilizumab antibodies in the confirmatory assay.

Table 2. Anti-TCZ antibody screening and confirmatory assay

SENSITIVITY OF ASSAY	7.81 ng-eq./mL for anti-TCZ antibodies (concentration in native serum)
CUT-POINT SENSITIVITY	46.7– 60.3 ng-eq./mL for anti-TCZ antibodies (concentration in native serum),
PRECISION (CV)	7.7% to 8.4% for anti-TCZ antibodies (screening assay) 5.0% to 6.5% for anti-TCZ antibodies (confirmatory assay)
ACCURACY	95.0% to 100.8% for anti-TCZ antibodies (screening assay) 95.4% to 102.5% for anti-TCZ antibodies (confirmatory assay)

In the placebo-controlled IV TCZ studies in the DMARD-IR population and the IV TCZ LTE studies commercially obtained sera from RA patients were used to generate the cut point. For Study WA19926, the immunogenicity assay methods were essentially the same with the following modification: the cut point used to define anti-TCZ antibody positivity was generated from baseline samples of the study population. Samples were initially evaluated using a cut point established from healthy volunteers; these were later re-evaluated using the cut point generated from the study patients' ADA values at baseline. This method corresponds to guidelines for immunogenicity testing [EMA/CHMP/BMWP/86289/2010 Guidance]. Screening and confirmation assay results presented below are based on the re-evaluation, including the results for patients who were positive for neutralizing antibody in samples that were ADA positive in the initial evaluation.

In Study WA19926, all patients had samples collected for anti-TCZ antibody testing at baseline, Week 52, and study exit, either prematurely or at the termination visit as per protocol. Blood samples, for patients who withdrew from the study due to events related to infusion reactions, were to be obtained at the time of the event and at least 6 weeks after the last infusion.

Methods of pharmacokinetic data analysis

Pivotal study WA199226

All PK/PD parameters were summarized descriptively on the basis of the PK-evaluable population. All study treatment groups were summarized in the PD summaries; however, in PK and PK-PD summaries, only those patients randomized to one of the TCZ treatment groups were included.

Patient's C_{wk2} (µg/mL), C_{min} (µg/mL), and C_{max} (µg/mL) were provided. C_{wk2} is the serum concentration at Day 14 after dosing in Week 2. C_{max} is the maximum observed plasma concentration immediately at the end of the infusion at Weeks 1 and 12. C_{min} is the pre-dose concentration at Weeks 4, 12, 16, 24, 36, 52, 76, and 104. AUC was not determined based on observed data due to the limited number of PK samples taken from each patient.

Summaries were also repeated for the following subgroups:

- DAS28 remission response status at Week 24 (responder, nonresponder)
- DAS28 remission response status at Week 52 (responder, nonresponder)
- mTSS progression at Week 52 (progressor, non-progressor)

Listings were repeated for the following subgroups:

- Patients with positive anti-TCZ antibody (human anti-human antibody) for screening, confirmative, and neutralizing assay result at Week 52
- Patients with positive anti-TCZ antibody for screening, confirmative, and neutralizing assay result at Week 104

- Patients who experienced a hypersensitivity that led to study withdrawal, with the results of anti-TCZ antibody assay testing taken at time of the event and at least 6 weeks after the hypersensitivity

Scatter plots were produced for DAS28 score versus C_{min} at Week 24 and mTSS versus C_{min} at Week 52. The PD parameters IL-6 and sIL-6R were summarized descriptively by visit (actual results and change from baseline results).

PK Comparison of pivotal study WA19926 with historical data

Graphical comparison of PK and PD results (4 mg/kg TCZ + MTX, 8 mg/kg TCZ + MTX) with Studies WA17822 (OPTION) and WA17823 (LITHE), which supported the initial RA filing, was provided. As the duration of WA17822 was only 24 weeks, PK-PD data from WA17823 will be the focus of such comparisons.

Additionally, comparison of 8 mg/kg TCZ monotherapy PK data with MRA012JP (SAMURAI) and WA17824 (AMBITION), and Comparison of 8 mg/kg TCZ + MTX PK data with that predicted from a prior population PK analysis based on results from four of the above studies (WA17822, WA17824, WA18062, and WA18063 [OPTION, AMBITION, RADIATE, TOWARD]) was provided.

Prior population PK analysis [Population PK Report No. 1031075]

This report was based on data from four of the pivotal Phase III studies supporting the initial filing (WA17822, WA17824, WA18062, and WA18063 [OPTION, AMBITION, RADIATE, TOWARD]). It should be noted that the population PK analysis included data from patients receiving TCZ both alone and in combination with MTX; however as part of the same analysis, MTX was not shown to have any impact on TCZ PK. This Population PK analysis, which is used for historical comparison, has previously been assessed in the context of the initial MAA.

Pharmacokinetics in target population

Pivotal study WA19926 (FUNCTION)

This study was a four-arm, double-blinded, double-dummy, randomized, parallel-group, pivotal Phase III study comparing treatment with TCZ (either in combination with MTX or as monotherapy) to MTX monotherapy. The study population consisted of patients with early, moderate to severe RA of less than 2 years duration who were naïve to treatment with both MTX and a biologic agent. Of the 1846 patients screened 1162 patients were randomized to treatment. Five patients withdrew prior to receiving any study treatment. Clinical pharmacology information from patients who completed 52 weeks (1 year) of treatment or withdrew prematurely from WA19926 is presented.

The pharmacokinetic-evaluable population included all patients who received at least one TCZ/placebo infusion and had at least one PK sample taken at any time during the study (up to Week 52 for the Week 52 data cut).

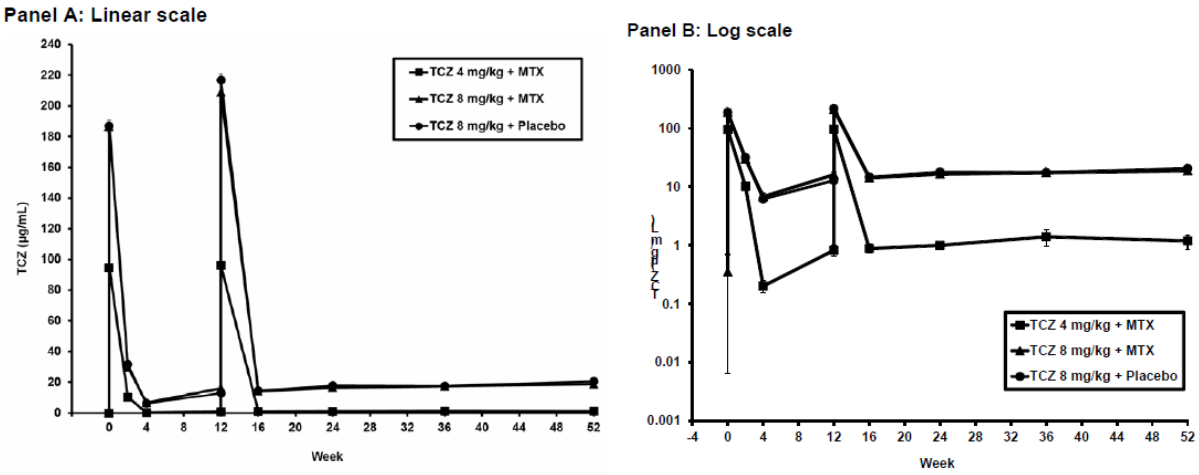
Pre-dose TCZ levels were measured at baseline and Weeks 4, 12, 16, 24, 36, and 52. Two samples were taken at the baseline and Week 12 visits; the first before dosing and the second immediately at the end of the TCZ/placebo infusion. An additional post-dose sample was taken at Week 2 (Day 14), representing a middosing interval sample after first dose.

Key findings – PK profile

Mean TCZ pre-dose concentrations appeared to stabilize after Week 16, with no clear trend for increases between Weeks 24 and 52 for all treatment groups. Mean C_{min} values from Weeks 24 to 52

following TCZ 4 mg/kg were about 16 fold lower on average than those seen following TCZ 8 mg/kg (with or without concomitant MTX). Concentration profiles for TCZ 8 mg/kg treatment groups with and without concomitant MTX were superimposable indicating no effect of concomitant MTX on TCZ exposure. Maximum serum TCZ concentrations in WA19926 were dose proportional following TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + MTX/placebo.

Figure 1. WA19926: Mean ± SEM TCZ Serum Concentration-Time Profiles Following IV Dosing Every Four Weeks for Patients in Actively Treated Study Arms



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

Table 3. WA19926: Summary of TCZ Serum Concentrations (µg/mL) Following IV Dosing Every Four Weeks for Patients in Actively Treated Study Arms

Week	Time		TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	TCZ 8 mg/kg + Placebo
0 (Baseline)	Pre-dose	N	281	289	292
		Mean ± SD	0.0 ± 0.0	0.35 ± 5.8	0.0 ± 0.0
		CV%	--	1669	--
0 (Baseline)	Post-dose (C_{max})	N	275	278	283
		Mean ± SD	94.8 ± 31.4	187 ± 67.3	187 ± 70.5
		CV%	33	36	38
2	Post-dose (C_{week2})	N	269	281	280
		Mean ± SD	10.2 ± 5.7	29.9 ± 10.4	31.6 ± 11.7
		CV%	56	35	37
4	Pre-dose (C_{min})	N	280	286	281
		Mean ± SD	0.2 ± 0.8	6.8 ± 17.8	6.2 ± 6.6
		CV%	389	264	108
12	Pre-dose (C_{min})	N	269	261	273
		Mean ± SD	0.8 ± 2.6	16.1 ± 27.5	12.8 ± 10.0
		CV%	323	170	78
12	Post-dose (C_{max})	N	249	240	254
		Mean ± SD	95.9 ± 38.7	209 ± 100	217 ± 66.3
		CV%	40	48	31
16	Pre-dose (C_{min})	N	262	253	263
		Mean ± SD	0.9 ± 2.3	14.2 ± 13.7	14.5 ± 11.9
		CV%	264	96	81
24	Pre-dose (C_{min})	N	246	251	257
		Mean ± SD	1.0 ± 2.5	16.5 ± 15.8	17.8 ± 23.6
		CV%	250	96	133
36	Pre-dose (C_{min})	N	220	214	223
		Mean ± SD	1.3 ± 6.6	17.4 ± 14.6	17.5 ± 13.5
		CV%	474	84	77
52	Pre-dose (C_{min})	N	218	214	222
		Mean ± SD	1.2 ± 4.8	18.7 ± 13.7	20.6 ± 25.3
		CV%	407	73	123

C_{min}=minimum observed plasma concentration; C_{max}=maximum observed plasma concentration; CV=coefficient of variation; MTX=methotrexate; SD=standard deviation; TCZ=tocilizumab

Comparison with previous results - Combination therapy with MTX

The table below presents observed PK parameters at Week 12 following 8 mg/kg TCZ+MTX from WA19926 compared to simulated C_{min} and C_{max} from the prior population PK analysis. It should be noted that the population PK analysis included data from patients receiving TCZ both alone and in combination with MTX; however as part of the same analysis, MTX was not shown to have any impact on TCZ PK. C_{max} values from WA19926 were similar to those from the population analysis based on historic data. C_{min} values were generally comparable as well, however the comparison was complicated by the high degree of variability in the data and the potential for error being introduced by use of scheduled rather than exact sample times when summarizing observed data from WA19926.

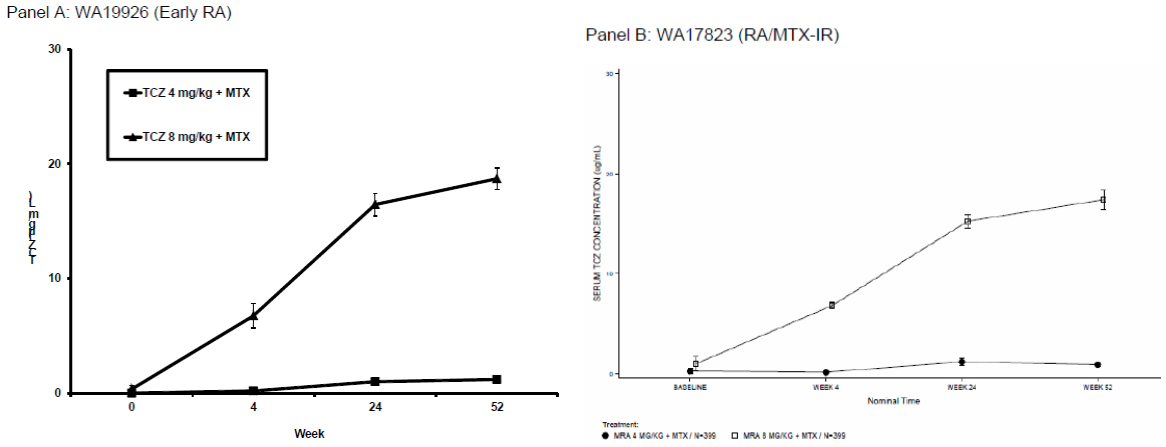
Table 4. Summary of Mean (± SD) Population Predicted C_{max} and C_{min} at Steady-State following 4 and 8 mg/kg TCZ every 4 Weeks compared to Observed Results at Week 12 from WA19926

Pharmacokinetic Parameter	4 mg/kg + MTX q4w		8 mg/kg + MTX q4w	
	WA19926	POP PK*	WA19926	POP PK*
C_{max} (µg/mL)	95.9 ± 38.7	88.3 ± 41.4	209 ± 100	183 ± 85.6
C_{min} (µg/mL)	0.8 ± 2.6	1.49 ± 2.13	16.1 ± 27.5	9.74 ± 10.5

*Analysis based on 7415 serum tocilizumab concentrations from a total of 1793 RA patients from 4 Phase III studies (WA17822, WA17824, WA18062 and WA18063)
C_{min}=minimum observed plasma concentration; C_{max}=maximum observed plasma concentration; MTX=methotrexate; POP PK=population pharmacokinetics; q4w=once every 4 weeks; TCZ=tocilizumab

Graphical comparison with WA17823 (LITHE) in combination therapy with MTX is presented below. Please note that the figure is limited by availability of data in common between studies and common time scale.

Figure 2. Mean ± SEM Pre-Dose TCZ (µg/mL) at Selected Visits

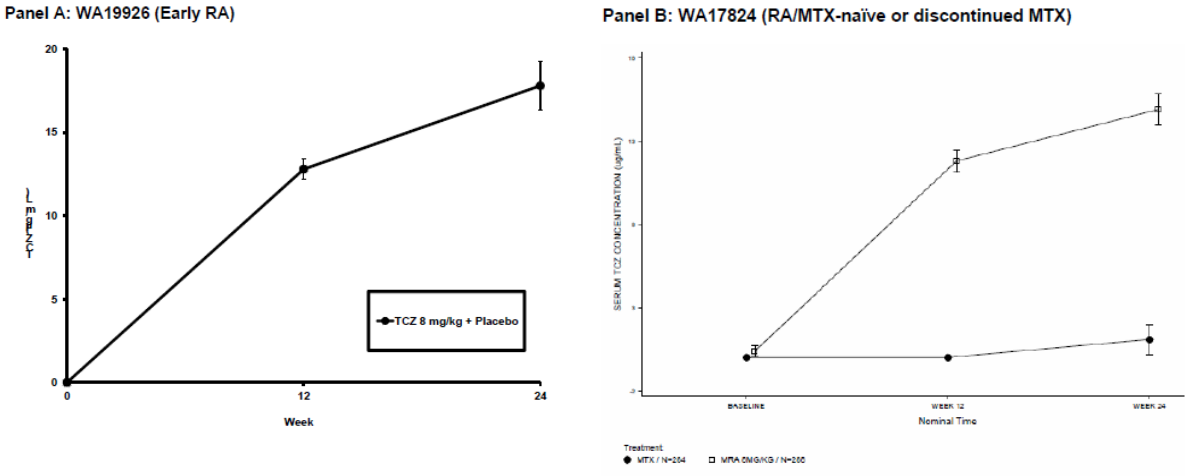


Comparison with previous results - Monotherapy

As discussed above, results from WA19926 indicated no effect of concomitant MTX on TCZ exposure in patients with early RA. A similar finding for lack of effect of concomitant MTX on TCZ PK (albeit limited to C_{min} and C_{max}) was noted also in the population PK analysis supporting the initial RA submission.

Graphical comparison with WA17824 (AMBITION) in monotherapy in presented below. It shows comparable TCZ levels from WA19926 at 8 mg/kg monotherapy versus those from the same treatment up to Week 24 from WA17824 (figure is limited by availability of data in common between studies and common time scale).

Figure 3. Mean ± SEM Pre-Dose TCZ (µg/mL) at Selected Visits



While week 12 and 24 TCZ level were 12.8-17.6 µg/ml in the pivotal study WA19926, in study WA17824 the levels were ~12.5-15.1 µg/ml respectively.

Steady-state pre-dose (C_{min}) concentrations from Clinical Study Report MRA012JP *(SAMURAI)* following treatment with 8 mg/kg TCZ monotherapy (i.e., without concomitant MTX) q4w ranged from approximately 12 to 15 µg/mL, slightly lower than those seen in global studies, as expected due to lower body weight in Japanese patients.

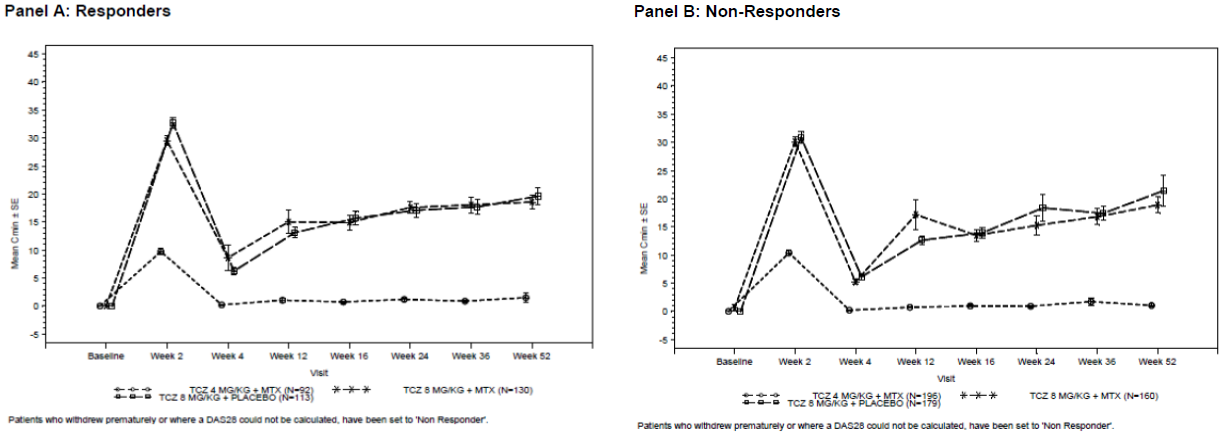
Body weight in the pivotal study was indeed higher (75±17 kg) than in study SAMURAI. Since it is known, that TCZ Cmax and C_{min} are weight dependent, this may account for the observed difference in C_{min}.

Special populations

Responders versus Non-Responders

The figure below presents pre-dose TCZ concentrations in patients based on their Disease Activity Score 28 (DAS28) response status at Week 24, and separates responders from non-responders. Patients with a remission response were defined as having a DAS28 score of <2.6. Week 2 concentrations (14 days following first dose) are also presented.

Figure 4. WA19926: Mean ± SEM Pre-Dose TCZ Concentrations (µg/mL) by DAS28 Remission Status at Week 24

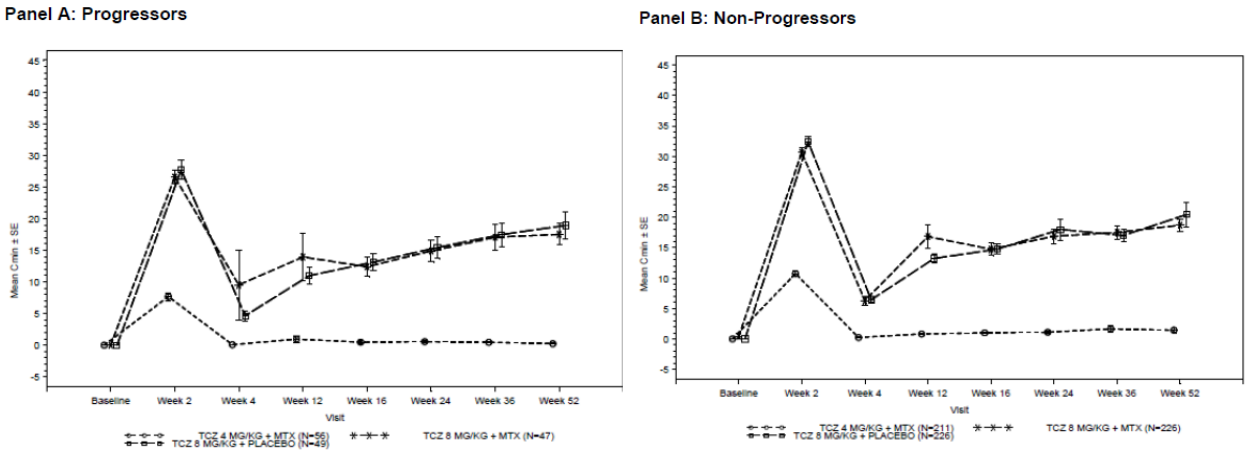


Profiles, by treatment group, for DAS28 responders were comparable to those for non-responders, indicating that there was no appreciable difference in TCZ exposures in the two patient sub-sets.

Although C_{max} values (concentrations at end of infusion following first dose and Week 12 dose) are not presented in the figure, review of these values also indicated no clear differences based on DAS28 response status. TCZ profiles, by treatment group, for DAS28 responders at Week 52 were also comparable to those for non-responders (figure not shown).

The figure below presents pre-dose TCZ concentration-time profiles in patients based on modified total Sharp score (mTSS) progression status at Week 52. Patients with an increase in mTSS from baseline were defined as progressors. Week 2 concentrations (14 days following first dose) are also presented.

Figure 5. WA19926: Mean ± SEM Pre-Dose* TCZ Concentrations (µg/mL) by Modified Total Sharp Score (mTSS) Progression Status at Week 52



PK profiles, by treatment group, for mTSS progressors were comparable to those for non-progressors, indicating that there was no difference in TCZ exposures in the two patient sub-sets. Although C_{max} values (concentrations at end of infusion following first dose and Week 12 dose) are not presented in the figures, review of these values also indicated no clear differences based on mTSS status.

Immunogenicity

The immunogenicity data from *pivotal Study WA19926* are presented, as well as supportive data from the placebo-controlled IV TCZ studies in the DMARD-IR population and data from the IV TCZ Long-Term Extension (LTE) studies all-exposure population. The safety dataset (referred to as the IV TCZ all exposure population) includes all data from patients who received at least 1 dose of TCZ in the clinical trial program.

Table 5. WA19926: Patients with Positive Anti-TCZ Assay Results

	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)
Baseline		n (%)		
Patients Tested at Baseline	274 (97.2)	275 (95.2)	283 (97.6)	285 (97.6)
Patients with a Positive Assay at Baseline:				
Screening Assay	12 (4.3)	16 (5.5)	16 (5.5)	12 (4.1)
Confirmation Assay	3 (1.1)	5 (1.7)	5 (1.7)	4 (1.4)
Neutralizing Assay	0	0	0	0
Post-Baseline		n (%)		
Patients Tested Post-Baseline	259 (91.8)	259 (89.6)	267 (92.1)	269 (92.1)
Patients with a Positive Assay Post-Baseline:		n (%)		
Screening Assay	18 (6.4)	12 (4.2)	12 (4.1)	17 (5.8)
Confirmation Assay	10 (3.5)	8 (2.8)	5 (1.7)	4 (1.4)
Neutralizing Assay	0	5 (1.7)	3 (1.0)	3 (1.0)
		n (%)		
Proportion of Patients Who Developed Anti-TCZ Antibodies During the Study*	9 (3.2%)	6 (2.2)	4 (1.4)	3 (1.0)

*Positive in both the screening and the confirmation assay post-baseline, and confirmation assay negative at baseline. The numbers of patients tested at baseline were used as the denominators.
MTX=methotrexate; TCZ=tocilizumab

Nine patients in the placebo + MTX group (3.2%) had positive results in the screening and confirmation assay post-baseline after testing confirmation assay-negative at baseline. This phenomenon of positive results for the placebo arm is consistent with what has been observed in previous studies.

Eleven patients in the TCZ treatment groups tested positive for neutralizing anti-TCZ antibodies post-baseline, however, 3 of these 11 patients (one patient in each treatment group) were not considered anti-TCZ neutralizing antibody positive by the MAH because they had a positive confirmation assay at baseline. None of these patients withdrew for insufficient therapeutic response or were classified as having experienced loss of efficacy. Of note, not considering anti-TCZ neutralization antibody positive patients who had confirmed binding antibody at baseline is not supported as they might have a cross-reacting antibody at baseline and in addition they might have developed neutralizing antibodies upon treatment.

For a comparison, immunogenicity data from previous studies is provided below.

Table 6. Immunogenicity data from TCZ-placebo controlled core studies

	WA17822		WA18062		WA18063	WA17823		WA17824
	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	TCZ 8 mg/kg + DMARD	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	TCZ 8 mg/kg monotherapy
Positive screening and confirmation assay [n (%)]	2 (1%)	5 (2.5%)	0	5 (3.0%)	9 (1.2%)	14 (3.5%)	4 (1.0%)	2 (0.7%)

A total of 3945 of the 4009 patients in the IV TCZ long term extension studies all-exposure population were screened for anti- TCZ antibodies at any time point. Serum samples from 334/3945 patients (8.3%) were positive in the screening assay. Serum samples of 44 of 3945 patients (1.1%) tested positive post-baseline in the *confirmation assay* for anti-TCZ antibodies; these patients are referred to as “anti-TCZ antibody positive.” Patients with a positive anti-TCZ antibody assay result were tested for neutralizing antibodies. A total of 59/3945 patients (1.5%) were post baseline positive for neutralizing antibodies. Of these, 40/59 (67.8%) patients had a positive test result by Week 24, and approximately 46/59 (78.0%) patients had a positive test result within the first year.

Effect of anti-TCZ antibodies on Pharmacokinetics

Pre-dose TCZ and sIL-6R serum concentrations were evaluated for 13 patients in Study WA19926 who developed anti-TCZ antibodies following initiation of treatment and also had available PK-PD data: 6 patients in the 4 mg/kg TCZ + MTX arm, 4 patients in the 8 mg/kg IV TCZ + MTX arm, and 3 patients in the 8 mg/kg TCZ + placebo arm. Eight of these 13 patients also developed neutralizing anti-TCZ antibodies. There was no trend for reduced TCZ concentrations in these patients when evaluating their PK profiles with individual dosing records and actual sampling times. This indicates that anti-TCZ antibodies had no effect on the PK of TCZ with the limited number of patients who developed anti-TCZ antibodies in this study.

Anaphylaxis / Hypersensitivity Reactions

Of the 19 patients who withdrew from Study WA19926 due to hypersensitivity AEs, 2 tested positive for anti-TCZ antibodies. One of the patients (in the TCZ 8 mg/kg + MTX group), who experienced an infusion-reaction AE developed anti-TCZ antibodies post-baseline. The other patient (in the TCZ 8 mg/kg + placebo group), who experienced muscle spasms, tested positive for anti-TCZ antibodies at baseline.

One anaphylactic reaction was observed in the TCZ 4 mg/kg + MTX group at the second infusion, and one serious hypersensitivity event leading to withdrawal was deemed an “infusion-related reaction” in the TCZ 8 mg/kg + placebo group. Both patients were negative for anti-TCZ antibodies in the confirmatory assay both at baseline and at scheduled testing post-baseline.

In the IV TCZ long term extension studies five of the 44 anti-TCZ antibody-positive patients experienced an anaphylactic reaction.

Effect of Neutralizing Anti-Tocilizumab Antibodies on Efficacy

Eleven patients in the TCZ treatment groups tested positive for neutralizing anti-TCZ antibodies post-baseline, however, 3 of these 11 patients (one patient in each treatment group) were not considered anti-TCZ neutralizing antibody positive because they had a positive confirmation assay at baseline. None of these patients withdrew due to insufficient therapeutic response or were classified as having experienced loss of efficacy (defined as those who withdrew as a result of insufficient therapeutic response after achieving at least a 50% improvement of American College of Rheumatology response criteria [ACR50] or European League Against Rheumatism (EULAR) good response).

There were an additional three patients who tested positive in the neutralizing assay post-baseline without a positive confirmation assay result (2 patients in the TCZ 8 mg/kg + MTX group, and 1 patient in the TCZ 8 mg/kg + placebo group). These three patients are also considered to have developed a neutralizing anti-TCZ antibody response.

For a comparison, immunogenicity data for the IV TCZ long term extension studies is summarised here. No relationship was observed between a positive result for neutralizing anti-TCZ antibodies and loss of efficacy. Neutralizing antibodies were also assessed in patients who withdrew due to insufficient therapeutic response (irrespective of the screening/confirmation test results). As lack of therapeutic response is a subjective assessment, it was also assessed how many of these patients had potentially experienced loss of efficacy, based on those patients who had achieved a ACR50 or DAS28 of the EULAR good response prior to withdrawing due to insufficient therapeutic response. Among the 206/4009 (5.1%) patients who withdrew for insufficient therapeutic response, 2 tested positive for post-baseline neutralizing antibodies. None of the 83 patients who had documented loss of efficacy tested positive for post-baseline neutralizing antibodies

Seroconversion in Patients Who Missed Two or More Consecutive Doses

Patients in Study WA19926 who missed at least two consecutive IV study drug infusions were tested for antibody development before and after missing two doses. A total of 150 patients underwent immunogenicity testing for this reason. Valid immunogenicity datasets (data from patients with a valid assay both prior to the first consecutive missed dose and after re-starting dosing) were obtained from 31 of these patients.

Table 7. Patients with Positive Anti-TCZ Assay Results Following Dose Interruptions (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)
Patients who missed 2 or more consecutive infusions and underwent testing; n (%)	17 (6.0)	33 (11.4)	52 (17.9)	48 (16.4)
Valid assays both prior to and after missed doses; n (%)	4 (1.4)	5 (1.7)	11 (3.8)	11(3.8)
Patients with negative result prior to missed doses and positive result after re-starting dosing:	Number of Patients (n)			
Screening Assay	1	0	1	2
Confirmation Assay	1	0	0	1
Neutralizing Assay	0	0	0	0
MTX=methotrexate; TCZ=tocilizumab				

Only 2 of these 31 patients had negative results in the confirmation assay prior to the first missed dose and then had a positive result in the confirmation after re-starting dosing (1 patient in the TCZ 8 mg/kg + placebo group, and 1 patient in the placebo + MTX group); both were negative in the neutralizing assay. Neither of these patients had AEs related to hypersensitivity or experienced loss of efficacy.

For a comparison, immunogenicity data for the IV TCZ long term extension studies is also summarised. Patients who missed more than 2 consecutive TCZ doses did not appear to seroconvert, and the rate of immunogenicity was not increased. Of the 3945 patients who were tested for anti-TCZ antibodies, a total of 1786 (45.2%) patients had at least one instance in which there were > 70 days between doses. These patients were considered to have missed ≥ 2 consecutive infusions. Of these, 849 patients (47.5%) had anti-TCZ antibody assays performed both before and after missing consecutive doses and could therefore be evaluated for the potential of missed doses resulting in anti-TCZ sero-conversion. The majority (830/849, 97.8%) of evaluable patients were negative (confirmation assay) for anti-TCZ antibodies, both before and after missing ≥ 2 consecutive doses. Nine patients (1.1% of the evaluable patients) were negative for anti-TCZ antibodies prior to their missed infusions and were positive after resuming infusions. However, another 7 patients (0.8%) were anti-TCZ positive before missing doses and anti- TCZ negative after resuming treatment.

Pharmacokinetic/Safety Relationships in Pivotal Study WA19926

The relationships between rates of all adverse events (AEs) or rates of infections and observed C_{min} at Week 24 are presented in the table below for the combined (TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + MTX) group, the TCZ 8 mg/kg + MTX group and the TCZ 8 mg/kg + placebo group.

Table 8. WA19926: Summary of Numbers and Rates of All AEs and Infection-Related AEs up to Week 52 by Week 24 C_{min} Quartiles

	TCZ 4 or 8 mg/kg + MTX*				TCZ 8 mg/kg + MTX				TCZ 8 mg/kg + Placebo			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number of patients	155	94	124	124	63	63	64	61	65	64	64	64
Mean C_{min} (µg/mL)	0.0	0.58	8.01	26.8	2.15	10.5	18.4	35.4	2.41	10.4	19.0	39.7
Median C_{min} (µg/mL)	0.0	0.31	8.15	23.8	1.18	10.2	18.4	30.7	1.98	10.9	18.7	31.0
Total Patient Years	133	92.8	121	122	60.9	61.9	63.3	60.0	63.8	63.6	63.3	63.0
Number of all AEs	612	406	530	554	247	249	237	313	243	268	221	235
AEs per 100 Patient Years	403	437	439	452	405	402	374	521	381	421	349	373
(95% CI)	(371-436)	(396-482)	(403-478)	(416-492)	(356-459)	(354-455)	(328-425)	(465-582)	(334-432)	(372-475)	(305-399)	(327-424)
Number of Infections and infestations	158	112	118	129	54	50	54	70	71	69	64	48
Infection AEs per 100 Patient Years	104	121	97.8	105	89	81	85	117	111	109	101	76
(95% CI)	(88-121)	(99-145)	(81-117)	(88-125)	(67-116)	(60-107)	(64-111)	(91-147)	(87-140)	(84-137)	(78-129)	(56-101)

*Includes all patients from 4mg/kg TCZ + MTX and 8mg/kg TCZ + MTX groups combined.
Q1-Q4 refer to the subgroups by C_{min} exposure quartile (from lowest to highest C_{min}).
Note: Only most frequent AEs were summarized in this table.
AE=adverse event; C_{min}=minimum observed plasma concentration; CI=confidence interval; MTX=methotrexate; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; TCZ=tocilizumab

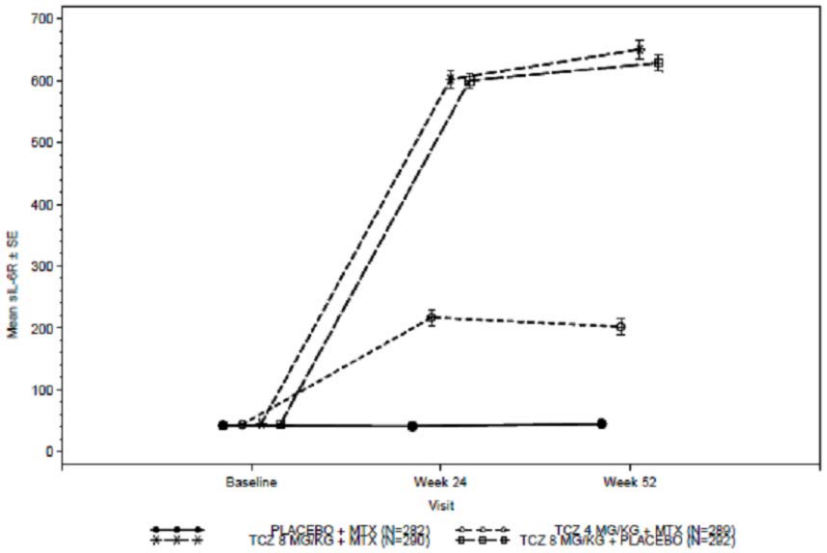
2.3.3. Pharmacodynamics

Pharmacokinetic/Biomarker Relationships in Pivotal Study WA19926

sIL-6R

Serum interleukin-6 receptor (sIL-6R) levels were measured at baseline and Weeks 24 and 52. Mean + SEM sIL-6R concentration time profiles are plotted in the figure below. Based on limited data available, following administration of TCZ, mean sIL-6R concentrations were elevated at Weeks 24 and 52 compared to baseline. The observed increases in sIL-6R were similar between the two TCZ 8 mg/kg treatment groups (with or without concomitant MTX), indicating no effect of concomitant MTX on sIL-6R. Increases in sIL-6R following TCZ 4 mg/kg + MTX were less than those seen at 8 mg/kg TCZ. Serum IL-6R levels in patients treated with MTX alone were unchanged compared to baseline.

Figure 6. WA19926: Mean ± SEM Pre-Dose sIL-6R (ng/mL) by Visit



ESR and CRP

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured at baseline and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 36 and 52. The mean ± SEM ESR profiles and the CRP profiles over time are displayed in the figures below.

A sustained decrease in ESR and normalization of CRP (to levels below 1 mg/dL) throughout Week 52 were achieved for both groups treated with 8 mg/kg TCZ (with or without concomitant MTX). The observed decreases in ESR and CRP were similar between the two 8 mg/kg TCZ treatment groups, indicating no effect of concomitant MTX on these PD markers.

But conversely reductions in ESR and CRP were also seen in patients treated with MTX alone. Decreases in ESR following treatment with MTX alone were less than those seen following 4 mg/kg TCZ + MTX. CRP concentrations in the MTX alone group were comparable to those seen following treatment with 4 mg/kg TCZ + MTX from Weeks 4 through 52.

Figure 7. WA19926: Mean ± SEM ESR (mm/hr) by Visit

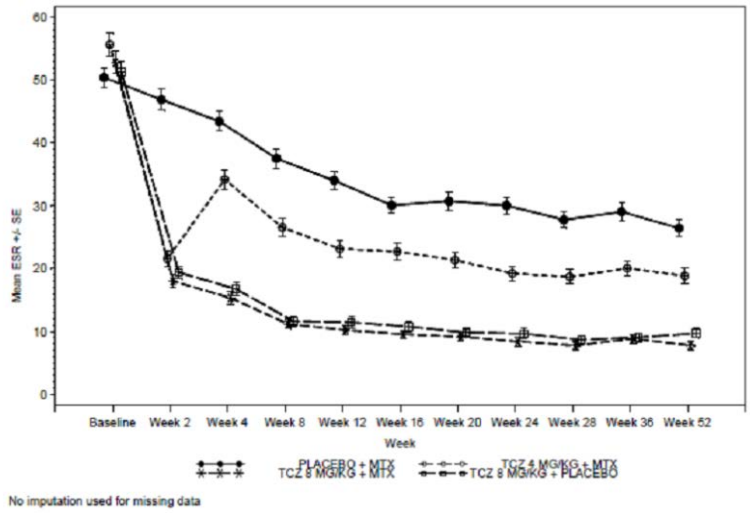
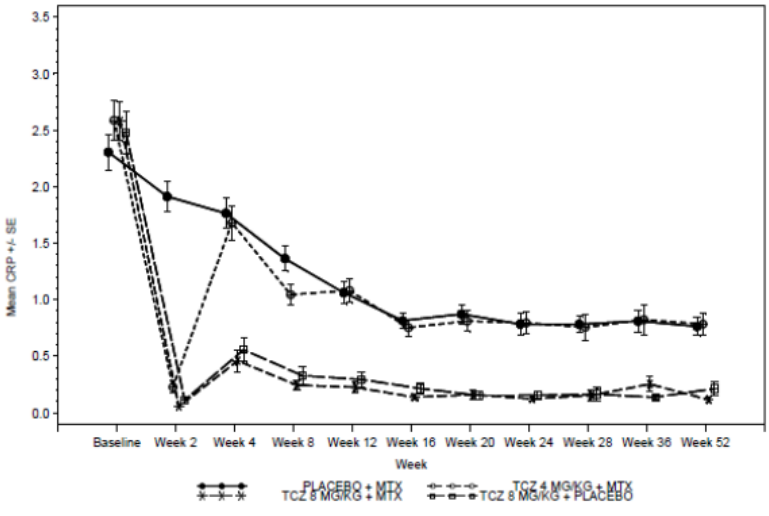


Figure 8. WA19926: Mean ± SEM CRP (mg/dL) by Visit



Pharmacokinetic/Efficacy Relationships in Pivotal Study WA19926

DAS28

A summary of the numbers and proportions of patients with DAS28 remission responses at Week 24 by Week 24 C_{min} quartiles is displayed in the table below. Patients with a remission response were defined as having a DAS28 score < 2.6. There was a large number of patients with undetectable (displayed as 0 µg/mL) TCZ concentrations at Week 24 in the 4 mg/kg TCZ + MTX group (n=138/246, approximately 56% of all observations in this group). As a result, the quartiles would have been extremely unbalanced with regard to sample size. Therefore, a quartile analysis was performed on a combination of patients participating in the TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + MTX groups instead of TCZ 4 mg/kg + MTX group alone; this analysis represents the continuum of all C_{min} values at Week 24 in patients receiving both dose levels of TCZ in combination with MTX. There remained a slight imbalance in the first and second quartiles of this "combination" group since a total of 155 patients had undetectable concentrations; this was a consequence of the low trough concentrations seen with TCZ 4 mg/kg dosing.

Table 9. WA19926: Patients with DAS28 Remission Response at Week 24 by Week 24 C_{min} Quartiles

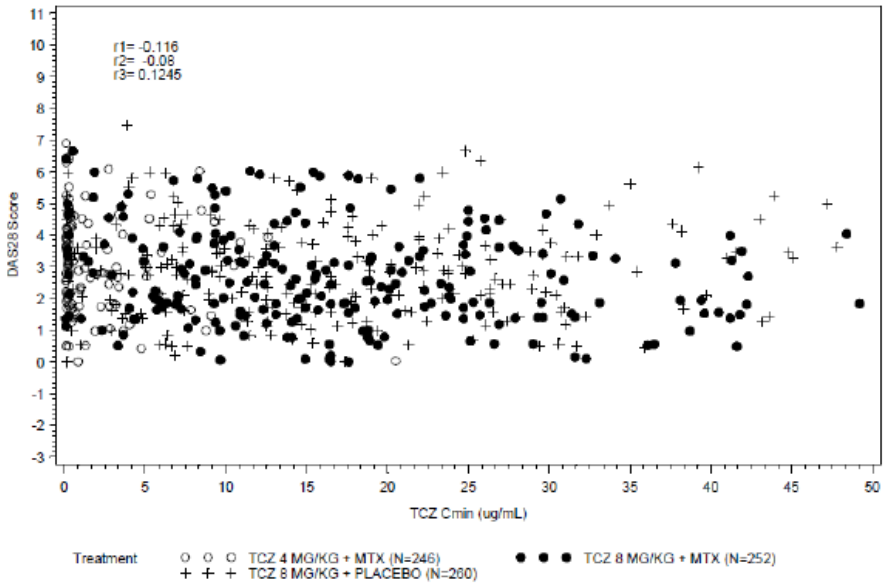
	TCZ 4 or 8 mg/kg + MTX*				TCZ 8 mg/kg + MTX				TCZ 8 mg/kg + Placebo			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number of patients	155	94	124	124	63	63	64	61	65	64	64	64
Mean C_{min} (µg/mL)	0.0	0.58	8.01	26.8	2.15	10.5	18.4	35.4	2.41	10.4	19.0	39.7
Median C_{min} (µg/mL)	0.0	0.31	8.15	23.8	1.18	10.2	18.4	30.7	1.98	10.9	18.7	31.0
DAS28 responders, n (%)	50 (32)	34 (36)	60 (48)	73 (59)	24 (38)	30 (48)	41 (64)	33 (54)	25 (39)	27 (42)	30 (47)	29 (45)

*Includes all patients from 4mg/kg TCZ + MTX and 8mg/kg TCZ + MTX groups combined.
Q1-Q4 refer to the subgroups by C_{min} exposure quartile (from lowest to highest C_{min}).
Remission: DAS28 < 2.6
C_{min}=minimum observed plasma concentration; DAS28=disease activity score 28; MTX=methotrexate; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; TCZ=tocilizumab

For the combined (TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + MTX) group, there was a clear trend for an increased proportion of DAS28 responders as C_{min} increased across the four quartiles. For the TCZ 8 mg/kg + MTX group and the TCZ 8 mg/kg + placebo group, there was a trend for an increased proportion of DAS28 responders as C_{min} quartiles increased from the first to third quartile, but no further increase afterwards; indicating the response may have reached a plateau. The DAS28 response rate for the TCZ 8 mg/kg + MTX group was higher than that for the TCZ 8 mg/kg + placebo group at the second, third and fourth quartiles, despite similar C_{min} levels, suggesting additional response due to the concomitant MTX treatment.

However, an alternative analysis yielded different conclusion. A scatter plot of DAS28 scores at Week 24 versus C_{min} at Week 24 is shown in the figure below.

Figure 9. WA19926: Scatter Plot of DAS28 Score and C_{min} at Week 24



r= : Pearson's Correlation Coefficient
Cmin is the predose concentration.
r1: TCZ 4 MG/KG + MTX; r2: TCZ 8 MG/KG + MTX; r3: TCZ 8 MG/KG + PLACEBO
LOCF used for tender and swollen joint counts, no imputation used for ESR and Patient's Global Assessment of Disease Activity VAS.
If ESR=0 then ESR=1 is substituted into the DAS28 calculation to enable a non-missing DAS28.

A clear correlation was not seen between raw DAS28 scores and C_{min} at Week 24 in patients in any of the active TCZ treatment groups. Indeed Pearson correlation coefficients ranged from -0.116 to 0.1245, further supporting the lack of clear correlation.

Modified Total Sharp Score

In study WA17823, the so called X-ray population consisted of patients who had available PK parameters, completed the 52 weeks treatment of the study and provided radiographic scores. Patients randomized to placebo that went on escape therapy were excluded from that population. The X-ray population consisted of 615 rheumatoid arthritis patients.

The relationship between the radiographic score changes from baseline and the cumulative TCZ AUC up to week 52 was assessed graphically by comparing the AUC in responders and non-responders. The responders were defined as patients with a score at week 52 below or equal to score at baseline and non-responders as patients with a score at week 52 above the score at baseline.

The plots of the time course of each radiographic score (in absolute change and in percentage change from baseline) for the placebo group and for the three categories of AUC (low, medium, high) are presented in the figures below for the erosion score, for the joint space narrowing score and for the modified Sharp score.

Figure 10. Erosion Score Change from Baseline over 52 Weeks for Placebo, Low, Medium and High Tocilizumab Exposure Categories

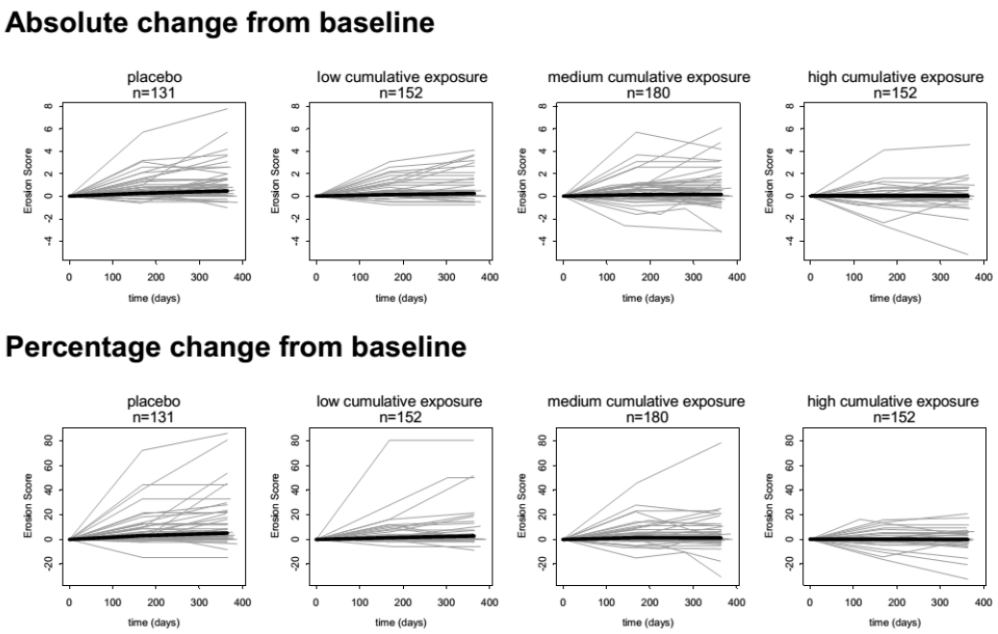


Figure 11. Joint Space Narrowing Score Change from Baseline over 52 Weeks for Placebo, Low, Medium and High Tocilizumab Exposure Categories

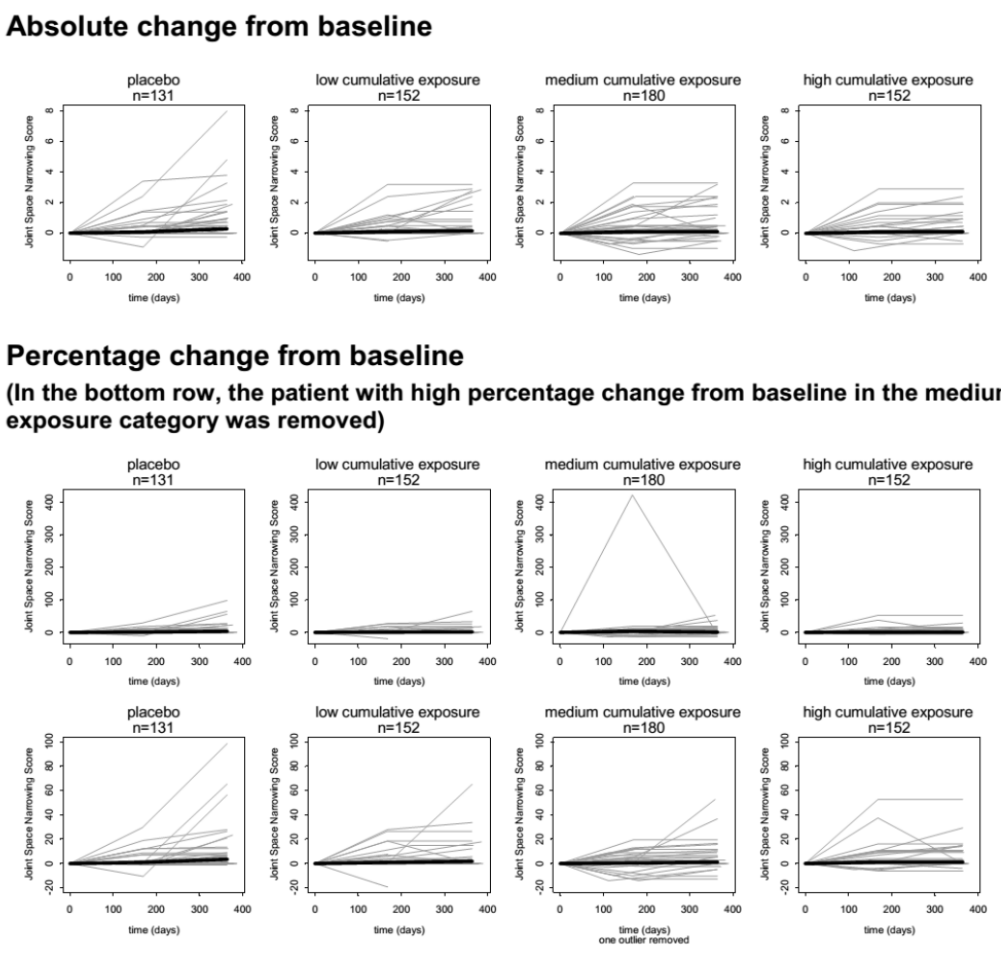
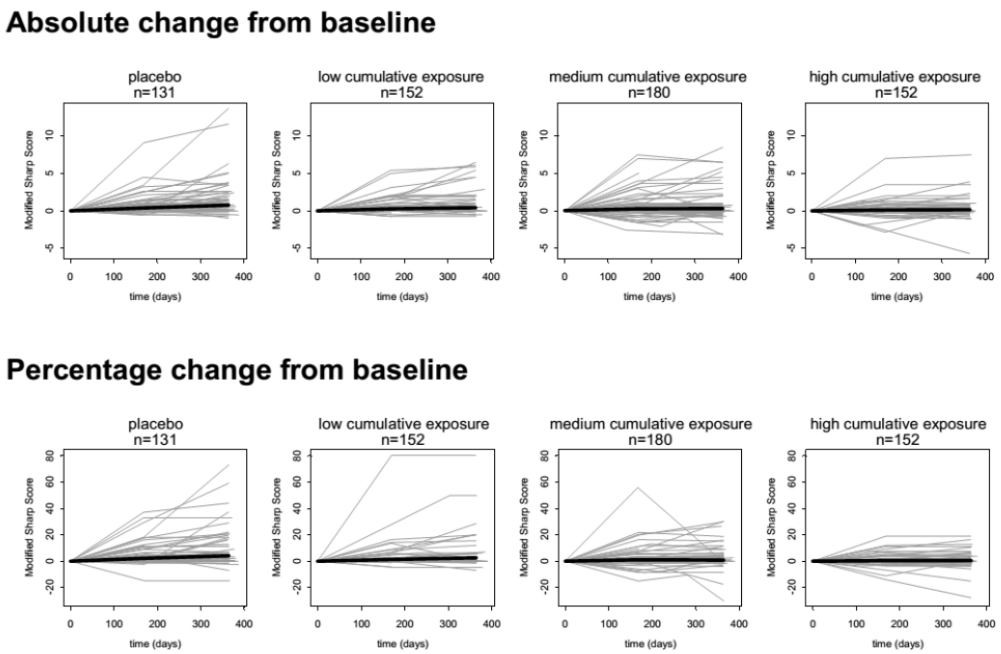


Figure 12. Modified Sharp Score Change from Baseline over 52 Weeks for Placebo, Low, Medium and High Tocilizumab Exposure Categories

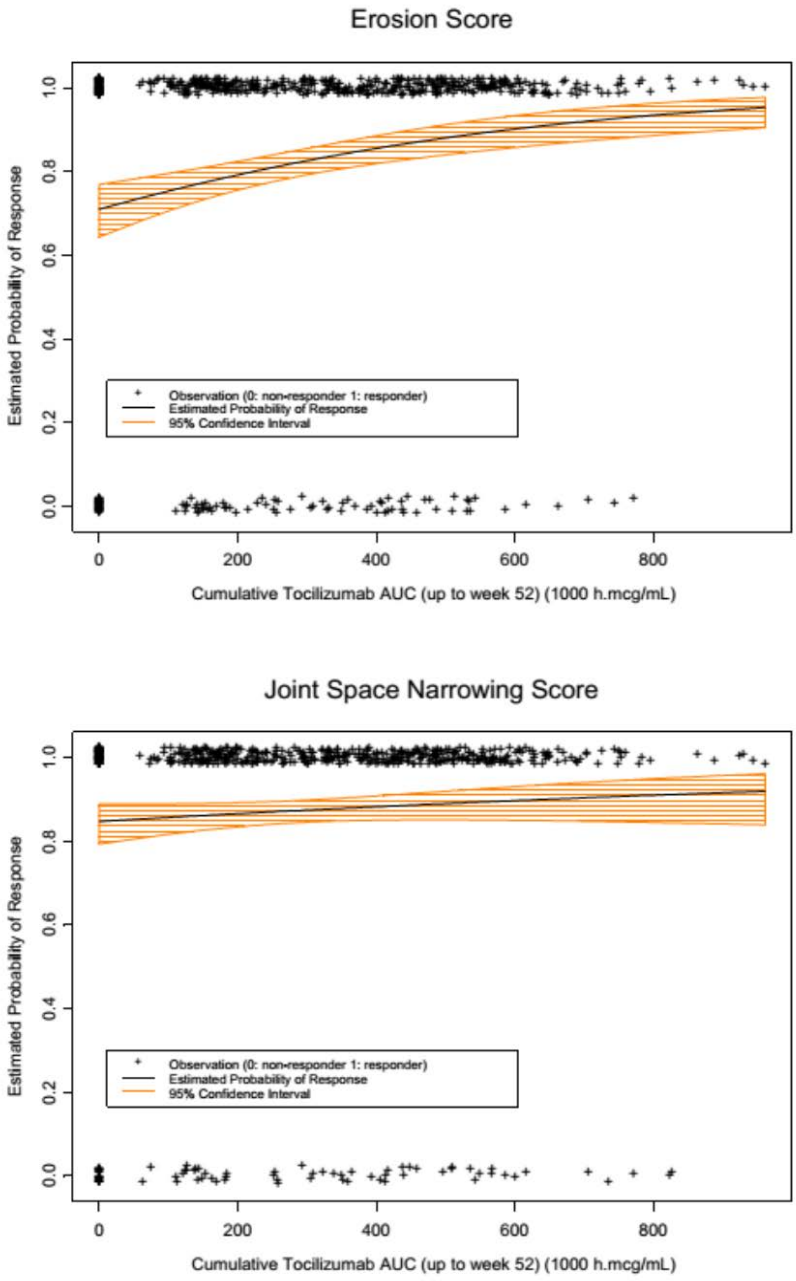


The visual inspection of the plots shows a slower progression (i.e. a decrease of the scores compared to baseline) of the erosion score in the medium and high AUC categories compared to placebo while no obvious difference of the joint space narrowing score can be noticed between the groups. The resultant of those two scores, the modified Sharp score seems to progress more slowly in highest exposure categories compared to the placebo group. See also the table below.

Table 10. WA19926: Comparison of Mean ± SD Change from Baseline mTSS and Trough TCZ concentrations at Week 52

	Placebo + MTX	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX	TCZ 8 mg/kg + Placebo
Pre-dose TCZ (µg/mL)	--	1.2 ± 4.8	18.7 ± 13.7	20.6 ± 25.3
Change in mTSS from baseline	1.14 ± 4.30	0.42 ± 2.93	0.08 ± 2.09	0.26 ± 1.87
mTSS=modified total Sharp score; MTX=methotrexate; TCZ=tocilizumab				

Figure 13. Comparison of cumulative tocilizumab AUC (up to week 52) in responders and non-responders



The Erosion score shows some dependency from the cumulative AUC while the Joint Space Narrowing Score clearly not.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

No separate PK/PD or immunogenicity study was conducted in the MTX-naïve RA population. PK/PD and immunogenicity parameters were measured in the pivotal study and summarized descriptively. The derived PK data were also compared with historical data from previously submitted pivotal studies. The set of PK parameters reported is reduced to C_{min}, C_{max} and C_{wk2}, since the sampling schedule did

not allow for a single dose PK profile. Thus only limited evidence can be derived from it, which is nevertheless commonly considered adequate for this type of application.

Validated assays were used for determination of IL-6sR and neutralizing anti-TCZ antibodies in serum as well as for anti-TCZ antibodies screening and confirmatory assay. Calibration and quality control were adequate, assay performance was satisfactory. The same assay formats appear to have been used as in the initial filing. Nevertheless, several methodological short comings were addressed, which result in uncertainties about the interpretation of results. The issue of further monitoring of immunogenicity is being addressed in the RMP.

The methodology for evaluation of immunogenicity has previously been assessed and agreed to. The change which was implemented by using the patient's own baseline value as cut point is considered adequate.

The PK profile in the early RA population relevant to the current variation was descriptively analysed in pivotal study WA19926 (FUNCTION) and compared to historical data, e.g. profile of TCZ in patients with RA as characterized in the original submission. Due to the limited number of samples per patient no AUC was derived directly in the current study.

In patients with early, moderate to severe RA of less than 2 years duration who were naïve to treatment with both MTX and a biologic agent:

- Mean TCZ pre-dose concentrations appeared to show no clear trend for further increases between Weeks 24 and 52 for all treatment groups.
- Mean C_{min} values from Weeks 24 to 52 following TCZ 4 mg/kg were about 16 fold lower on average than those seen following TCZ 8 mg/kg (with or without concomitant MTX). This is more than what has been described in the Population PK analysis of pivotal studies from previous filings and apparently due to the higher concentration level following TCZ 8 mg/kg in study WA19926. The MAH was asked to comment on the discrepancy in C_{min} at steady state of the pivotal study (~ 18 µg/ml) and the Population PK report (based on four previously filed pivotal studies, C_{trough} of 9.74 ± 10.5 µg/ml).
- Concentration profiles for TCZ 8 mg/kg treatment groups with and without concomitant MTX were superimposable indicating no effect of concomitant MTX on TCZ exposure. This is in alignment with the previous Population PK report findings.
- Maximum serum TCZ concentrations in WA19926 were dose proportional following TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + MTX/placebo.

It is acknowledged that the variability of the concentration parameters is extremely high limiting the reliability of the information that can be derived from it. Overall, the PK data from the pivotal study are sparse given the restricted sampling time points in the individual patient, the reduced set of PK parameters available and the descriptive analysis.

Furthermore, there also seems to be a discrepancy between the C_{trough} levels derived from the Population PK analysis of the previous phase III studies, which are used for comparison, and the actually measured values in some of these studies. In contrast to the Population PK analysis (based on studies WA17822, WA17824, WA18062, and WA18063; OPTION, AMBITION, RADIATE, TOWARD), which suggests a C_{trough} at steady state of 9.74 µg/ml, study WA17823 (LITHE) in MTX-inadequate responders indicates a higher C_{min} level (week 24-week52: ~15.5-17.6 µg/ml) comparable to the current pivotal study. Similarly, a graphical comparison indicates that TCZ administered as monotherapy (8 mg/kg) results in concentrations at week 12 and week 24 in the range of 13-17 µg/ml that are comparable in MTX naïve RA patients (current pivotal trial) and the RA patients that discontinued MTX (WA17824, AMBITION).

Taken together, these observations suggest that the Population PK analysis may not adequately reflect C_{trough} levels in the previously submitted phase III studies, which are used for comparison in the current variation application and is currently reflected in the SmPC. Of note, on 6 May 2014 the MAH has submitted a type II variation to update the PK information in the SmPC. Assessment of that variation is ongoing.

The PK profiles of TCZ 8 mg/kg with/out MTX and of TCZ 4 mg/kg + MTX are comparable between patients, who showed a response in terms of reduction of DAS 28 score to < 2.6 at week 2, and non-responders. There is also no difference in the PK profiles of TCZ 8 mg/kg with/out MTX and of TCZ 4 mg/kg + MTX between patients, who progressed in terms of mTSS (week52) and those who experienced no progression.

In the pivotal study, the numbers of patients who were considered to have developed post-baseline anti-TCZ antibodies in the TCZ treatment groups up to Week 52 ranged from approximately 1% to 2%. The percentage of patients who developed neutralizing anti-TCZ antibodies was also low (1.0% – 1.7%). Overall, the submitted results suggest that immunogenicity of all three dose cohort (TCZ 4mg/kg, TCZ 8 mg/kg ± MTX) was in the same range as previously observed in other RA studies at these dose regimens. However, the results of immunogenicity assessments in the placebo group of study WA19926 are puzzling as the percentage of patients who developed TCZ antibodies was higher than in any of TCZ groups. A few patients were found positive for TCZ binding antibody at baseline. In MAH's opinion this phenomenon is likely due to the potential biological interferences (e.g. autoantibodies) in the screening/confirmation assays, indicating that rheumatoid factor (RF) has the potential to cause false positive results. To explain the observations, the possible interference of RF with the detection of anti-TCZ antibody needs to be explored in more details. The CHMP therefore recommends the MAH to address the possible interference by RF and conduct a study to support the sensitivity and specificity of the assays used in the immunogenicity testing for assessing the possible immunogenicity of TCZ. The MAH has confirmed that it will further investigate the RF interference in the immunogenicity assay, providing full study details in Q4 2014 and the study results in Q2 2015.

Neutralizing capacity appears more specific since no neutralizing antibody was found among patients not treated by TCZ.

The effect of anti-TCZ antibodies on PK was evaluated in only 13 patients, of which eight had developed neutralizing antibodies. The MAH reports that there was no trend for reduced TCZ concentration. However, given this very low number no conclusions should be drawn from this.

Only one (1/17; e.g. 5.9%) of the patients, who developed anti-TCZ antibodies post-baseline, experienced an infusion reaction (but no anaphylactic reaction). This patient was 1 of 3 patients, who developed ADAs under monotherapy with TCZ. In comparison, in the IV TCZ long term extension studies about twice as many patients with ADA experienced anaphylaxis (5/44, 11.4%). In the pivotal study, the overall incidence of TCZ related anaphylaxis/hypersensitivity is low (0.12%), even in the 8 mg/kg TCZ group (0.3%). The overall incidence of ADA related anaphylaxis/hypersensitivity is low (0.13%), even in the 8 mg/kg TCZ group (0.3%). It is recommended that patients who experienced anaphylactic/hypersensitivity reactions should be tested by the neutralization assay as well.

The link between neutralizing ADAs against TCZ and a loss of efficacy is rather weak, since neither in the pivotal study nor in the long term extension studies any of the patients with a post-baseline positive neutralizing ADA test results had documented loss of efficacy.

Sero-conversion was documented in 1/31 evaluable patients (3.2%) treated with TCZ in the pivotal study and who missed at least two consecutive IV infusions, but it did not result in the development of neutralizing ADAs. This is higher than the incidence observed in the IV TCZ long term studies (9/849, 1.1%), but the difference may have to be attributed to the low number of the evaluable patients in the

pivotal study. Overall, sero-conversion is not expected to constitute a major aspect of or effect on safety and efficacy.

There is a trend that the risk of having infection is increased by about 20% in the highest exposure (Q4) group when patients are treated with TCZ 8 mg/kg and MTX. This might be understood based on general principles of pharmacology. However, given that the range of infection AEs/100 patient years are roughly comparable across the treatment regimens and fluctuate quite substantially (with the 95% CIs of the quartiles overlapping), the increase in the 4th concentration quartile in the TCZ 8 mg/kg + MTX group may also just be a chance finding.

Pharmacodynamics

There were two goals of the PD and PK/PD measurements. First was to demonstrate that TCZ has additional effect to MTX in patients previously not treated with MTX. Second was to show that early treatment with TCZ can halt or even reverse the disease progression based on radiological assessments. Such claims could be demonstrated if positive concentration - response (PK/PD) relationship was shown (as proof of efficacy and, additionally, guiding the correct dosing). The MAH measured several markers of the disease symptoms and progression, but the relevance of the markers are markedly different regarding to the short and long-term clinical effects.

The concentration of serum interleukin-6 receptor (sIL-6R) is directly related to TCZ exposure, but a firm link between sIL-6R level and disease activity or clinical response has not been established yet. The increase in serum sIL-6R seen after administration of TCZ is probably due to the formation of a sIL-6R/TCZ immune complex which cannot be eliminated by its normal receptor-mediated pathway.

CRP seems to be a better predictor because CRP is mainly produced by hepatocytes, which express cell-surface IL-6R. CRP therefore seems to be a surrogate marker for TCZ levels that are high enough to inhibit the effects of IL-6 in patients.

The ESR is governed by the balance between pro-sedimentation factors, mainly fibrinogen, and those factors resisting sedimentation, namely the negative charge of the erythrocytes (zeta potential). When an inflammatory process is present, the high proportion of fibrinogen in the blood causes red blood cells to stick to each other. The ESR is increased by any inflammation.

The progression of RA was followed using the Disease Activity Score of 28 joints (DAS28). It is widely used as an indicator of RA disease activity and response to treatment, but is not always a reliable indicator of treatment effect. Note that ESR (or CRP) is directly linked to DAS28.

The modified total Sharp score (mTSS) measures peripheral joint involvement. It is an index based on radiographs and directly linked to the clinical outcome.

For the stated purposes data were collected in two studies:

- Study WA19926 which is of the pivotal Phase III study (WA19926) supporting this Type II application
- Study WA17823 which was a study in moderate to severe active rheumatoid arthritis. Thus this study has only a supporting role in this Type II variation, as the study and target patient groups of Type II application are different. The planned study period of Study WA17823 was two years however only results of an interim analysis (results after 52 weeks) were submitted.

The scope of PK/PD analysis was very limited because it is essentially narrowed down to investigating the relationship between C_{min} and a PD parameter, while C_{min} is not a good predictor of the overall exposure due to the nonlinear features of TCZ pharmacokinetics. Therefore the PK sampling strategy

was very far from being optimal, which potentially can explain why the MAH could not demonstrate a robust concentration-effect relationship.

sIL-6R levels similarly increased in the two TCZ 8 mg/kg treatment groups (with or without concomitant MTX) in study WA 19926. This was expected because sIL-6R levels have been shown directly related to the TCZ mode of action and not to the therapeutic outcome.

A sustained decrease in ESR and normalization of CRP (to levels below 1 mg/dL) throughout Week 52 were achieved for both groups treated with 8 mg/kg TCZ. The observed decreases in ESR and CRP were similar between the two 8 mg/kg TCZ treatment groups (with or without concomitant MTX). This is in contrast with results for MTX alone, which also was effective. However, some differences between CRP and ESR were observed. The ESR decrease following treatment with MTX alone was less than that seen following 4 mg/kg TCZ + MTX while CRP concentrations in the only MTX group were comparable with values following treatment with 4 mg/kg TCZ + MTX. The most plausible assumption to explain these findings is that the maximum possible (plateau) level has been achieved alone with the dose of 8 mg/kg TCZ that is why the additionally administered MTX apparently had no additional effect on ESR and CRP. The same is true for CRP and 4 mg/kg dose is sufficient to reach the maximum effect.

A scatter plot of DAS28 scores at Week 24 versus C_{min} at Week 24 was presented. No clear correlation is seen between raw DAS28 scores and C_{min} at Week 24 in patients in any of the active TCZ treatment groups. Pearson correlation coefficients ranged from -0.116 to 0.1245, further supporting the lack of a clear correlation. Still, using an alternative statistical approach, some tendency between C_{min} and DAS28 could have been demonstrated. A summary of the numbers and proportions of patients with DAS28 remission responses at Week 24 by Week 24 C_{min} quartiles was also presented. Quartile analysis was performed on a combination of patients participating in the TCZ 4 mg/kg + MTX and TCZ 8 mg/kg + MTX groups. The results show a trend for an increased proportion of DAS28 responders as C_{min} quartiles increased from the first to third quartile, but no further increase afterwards. This indicates that the response may have reached a plateau. The DAS28 response rate for the TCZ 8 mg/kg + MTX group was higher than that for the TCZ 8 mg/kg + placebo group at the second, third and fourth quartiles, despite similar C_{min} levels, suggesting additional response due to the concomitant MTX treatment.

On the other hand, mTSS does not show the plateau effect seen on inflammatory markers and DAS28 in study WA19926. The results suggest that TCZ+MTX combination is more effective than giving MTX or TCZ (8 mg/kg) alone. However, mTSS is also a composite score and it seems only one of its components (bone erosion) is slowed down due to treatment. The other component, progression of narrowing of the joint space, has not been affected at all.

It is noted that higher exposure is associated also with additional risk – infection rate might be increased by about 20% in the highest quartile group when the patients are treated with TCZ 8 mg/kg and MTX.

The MAH suggested that early treatment with TCZ might slow down or even reverse the joint destruction process. The radiographic results of study WA17823 do not directly support this claim because in study WA17823 patients with moderate to severe active rheumatoid arthritis were involved. By the protocol study WA17823 lasted for two years with an additional follow-up period. As presented above it seems that in some patients the bone and joint destruction process has been halted or even reversed after one year of TCZ treatment. It would be interesting to know that TCZ stopped the destruction process or just delayed it. However, the final closing report of WA17823 has not been submitted.

2.3.5. Conclusions on clinical pharmacology

Overall, the provided results, albeit limited and descriptive only, appear to indicate comparable PK of TCZ and immunogenicity between the MTX-naïve RA population and already approved RA populations.

Firm conclusions cannot be drawn based on the results of the PK-PD analysis. The MAH could not demonstrate statistically significant concentration-effect relationship between TCZ exposures and the clinically decisive parameters such as DAS28 and mTSS. By visual inspection of the data (results of studies WA19926 and WA17823), a very weak positive tendency can be observed between TCZ exposures and clinical effects. Based on that, it might be hypothetically assumed, that larger doses are required to slow down disease progression as seen by X-ray than to achieve remission (based on DAS28). However, higher exposure is associated with additional risk (infection rate might be increased by about 20% in the highest quartile group when the patients are treated with TCZ 8 mg/kg and MTX).

2.4. Clinical efficacy

The clinical efficacy data provided consist of the results of the Week-52 data of the pivotal Phase III trial, WA19926 (FUNCTION). Supporting data was provided by studies, WA17824 and Chugai Study MRA012JP. In addition, data concerning persistence of efficacy from the WA17823 (LITHE) study and from long-term extension (LTE) in early RA and monotherapy subgroups were also presented.

Table 11. Summary of Studies Contributing to Efficacy Evaluation

Study/ No. of Pts Randomized	Patient Population	Primary Endpoint	Design and Duration	Treatment
WA19926 (FUNCTION) (pivotal study) **N = 1157**	MTX-naïve patients with early (≤ 2 yrs since diagnosis), moderate to severe active RA	DAS28 remission at wk 24	DB, DD, R, PC: 104-wk (interim analysis at wk 52)	**4 arm study**: TCZ 4 or 8 mg/kg IV q4w + MTX 7.5–20 mg/wk, or TCZ 8 mg/kg IV q4w + oral placebo weekly **or** placebo IV q4w + MTX 7.5–20 mg/wk
WA17824 (AMBITION) (supportive study) **N=673**	Active RA; MTX naïve or MTX discontinued but not due to lack of efficacy or toxic effect	ACR20 at wk 24	DB, DD, R, PC: 24-wk	**2 arm study:** TCZ 8 mg/kg IV q4w **or** MTX 7.5–20 mg/wk
MRA012JP (SAMURAI) (supportive study) **N=302**	Active RA (disease duration at least 6 mos and < 5 yrs) in DMARD inadequate responders	Change in vdH mTSS at wk 52	OL, R, x-ray reader blinded: 52-wk	**2 arm study:** TCZ 8 mg/kg IV q4w **or** conventional DMARDs
WA17823 (LITHE) (historical study providing long-term data) **N=1196**	Moderate to severe active RA in MTX inadequate responders	ACR20 at wk24; change in Genant mTSS, AUC of HAQ-DI at wks 52 and 104	DB, R, PC: *DB:52-wk; OL: 104-wk*	**3 arm study:** TCZ 4 or 8 mg/kg **or** placebo IV q4w + MTX 10–25 mg/wk
All-Exposure Population N=4171	Patients receiving at least one dose of TCZ in WA17822, WA17823, WA17824, WA18062, WA18063, WA18695, WA18696, WA19924, WP18663	Long-term safety/efficacy	Patients taking at least one dose of blinded or OL TCZ	**Single arm:** TCZ 4 or 8 mg/kg placebo IV q4w ± MTX **or** DMARDs

ACR20 = American College of Rheumatology 20% improvement criteria, AUC = area under the curve, DAS28 = Disease Activity Score 28, DB = double-blind, DD = double dummy, DMARD = disease-modifying antirheumatic drug, HAQ-DI = health assessment questionnaire - Disability Index, IV = intravenous, LTE = long-term extension, mTSS = modified total Sharp score, MTX = methotrexate, OL = open label, PC = placebo-controlled, q4w = every 4 weeks, R = randomized, RA = rheumatoid arthritis, TCZ = tocililumab, vDH = van Der Heijde.

2.4.1. Main study

Study WA19926

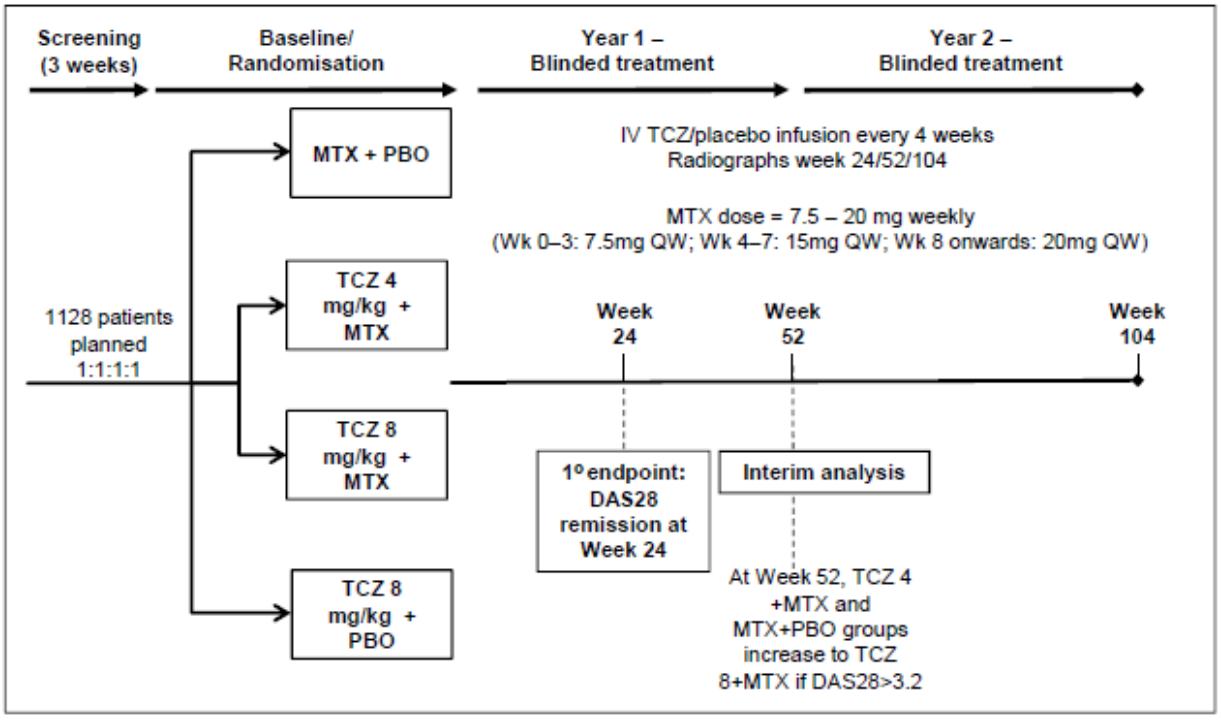
Methods

Study WA19926 was a multi-centre, randomized, double-blind, and parallel-group study of the safety, disease remission and prevention of structural joint damage during treatment with tocilizumab, as a

monotherapy and in combination with methotrexate, versus methotrexate in patients with early, moderate-to-severe rheumatoid arthritis.

The study duration is 2 years. In this submission the Week 52 data were reported. Data from Week 104 will be reported at a later time.

Figure 14. WA19926 Study Design



At Week 52, patients in the TCZ 4 mg/kg + MTX and placebo + MTX treatment groups who had a DAS28 of ≥ 3.2 could receive escape therapy with TCZ 8 mg/kg + MTX.

Study participants

The target population for this study was adult patients with moderate-to-severe active early RA who were naïve to treatment with both MTX and a biologic agent. RA was diagnosed according to the 1987 revised American College of Rheumatology (ACR) criteria.

Eligible patients had:

- 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) both at screening and baseline visits
- Erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr or C reactive protein (CRP) ≥ 10 mg/L at screening visit only
- 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)

The number of patients negative for both RF and anti-CCP Ab was limited to 20% of the total study population.

Patients were ineligible if they had received previous treatment with MTX or a biologic agent. All other DMARD therapies were discontinued prior to study entry.

Treatments

The following treatments were applied in this study:

- TCZ 8 mg/kg + MTX
- TCZ 8 mg/kg + placebo (TCZ 8 mg/kg monotherapy)
- TCZ 4 mg/kg + MTX
- Placebo + MTX (MTX monotherapy)

TCZ was administered every four weeks for the duration of the study. MTX was administered 7.5 – 20 mg/week oral tablets for the duration of the study.

During the study, patients were allowed to continue to receive a background corticosteroid dose of ≤10 mg/day of prednisone (or equivalent). Doses had to continue unchanged for at least the first 6 months of the study and remain stable for the duration of the study.

At study entry, stable oral NSAID doses were allowed and continued unchanged for at least the first 6 months of the study and remained stable for the duration of the study.

Analgesics other than NSAIDs were permitted for pain management as required. However, patients were not allowed to take analgesics within 12 hours prior to a visit.

Objectives

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

Additional objectives included assessment of 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.

Outcomes/endpoints

Primary endpoint

The primary endpoint of the study was proportion of patients who achieved Disease Activity Score (DAS) 28 remission (DAS28 < 2.6) at 6 months.

The primary comparison was between the TCZ 8 mg/kg + MTX and placebo + MTX treatment groups.

Secondary endpoints

Secondary endpoints included:

- DAS28 remission response at week 52
- ACR20, ACR50, ACR70 response at Week 24 and Week 52
- Change from baseline in mTSS at Week 52
- Change from baseline in in modified Sharp erosion score at Week 52

- Change from baseline in modified Sharp Joint Space Narrowing (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 (HAQDI) 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

Further exploratory parameters were also analysed.

Sample size

Based on data from earlier studies in patients with early RA, a DAS28 remission response rate at week 24 of 16% was assumed for the placebo + MTX group and 26% for patients with TCZ 8 mg/kg + MTX. It was calculated that 282 patients per group would allow detecting such a difference with 80% power in a two-sided test at a significance level of 5%. Based on these calculations a total of 1128 patients were to be included into the study. Accounting for 10% for patients with insufficient radiographic data, the planned sample size of 282 patients per group was estimated also to provide about 98% power to detect a mean difference of 2.17 units in change from baseline in modified total Sharp score between the TCZ 8 mg/kg + MTX treatment group and the Placebo + MTX treatment group in a two-sided test at 5% significant level.

Randomisation

Patients were randomized in a 1:1:1:1 ratio to one of the four treatment groups. Randomization was stratified by serologic status (RF and/or anti-CCP Ab positivity) and by geographic region (Europe, North America, South America, ROW).

Blinding (masking)

According protocol and CSR study WA19926 was a double blind study.

To minimize the risk of unblinding of investigational staff, monitors, central services (central lab), and Roche study management team during the remainder of the study, the week 52 data analysis was performed by a selected group of Sponsor's team members only and was not to be communicated to investigational staff, monitors or central services. Furthermore the week 104 analyses do not plan for any formal comparison between treatment arms.

Statistical methods

The between treatment group comparisons (TCZ groups versus placebo + MTX) for the primary and secondary endpoints was based on the following methods:

- Binary response variables, such as the DAS28 response at week 24, were primarily analysed using a logistic regression model with the stratification factors at randomisation as covariates. In addition Cochran-Mantel-Haenszel-test stratified for the strata used in randomisation was applied.
- The change from baseline in the radiographic scores at week 52 was compared between the TCZ treatment groups and the placebo + MTX treatment group using a non-parametric analysis of covariance.

- Continuous variables other than the radiographic scores were analyzed using an analysis of covariance model, with treatment group, the baseline score, and the stratification factors applied at randomization included in the model.
- Treatment effects were described by means of 95%-confidence intervals.

The TCZ groups were compared to the placebo+MTX group for superiority based on the ITT population. All statistical (null-) hypotheses (of no treatment effect) for the primary and secondary endpoints and treatment comparisons were tested at the 5% significance level ($\alpha = 0.05$) against two-sided alternatives. The analyses of endpoints and treatment comparisons were performed in a pre-defined, fixed sequential order to control the type I error rate for multiple comparisons. For comparisons that occurred after the hierarchical chain break, statistical significance is not claimed.

The primary efficacy analysis was the comparison of DAS28 remission response rate at week 24 between the TCZ 8 mg/kg + MTX and placebo + MTX treatment groups. The TCZ 8 mg/kg + placebo and TCZ 4 mg/kg + MTX treatment groups were also compared with the placebo + MTX group when the primary comparison null hypothesis was rejected. These treatment comparisons were included into the hierarchical testing procedure (at positions 13 and 18 respectively). Please see full list of hierarchical testing in the results section.

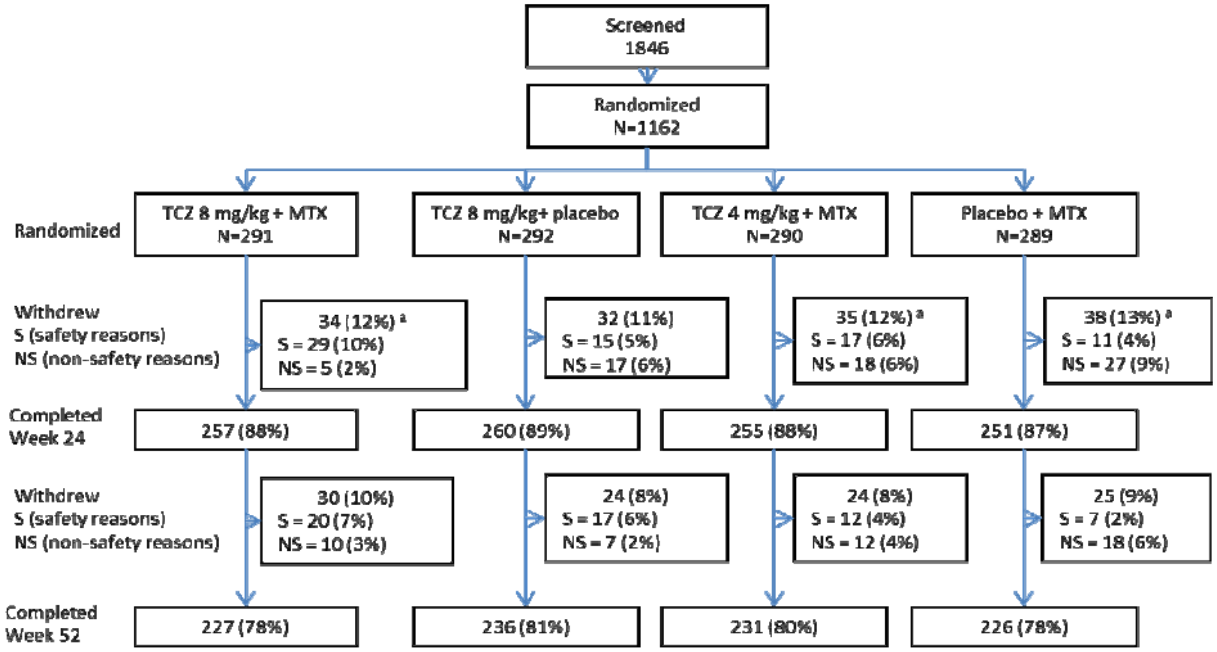
For binary endpoints missing values were considered as non-responder; in case of radiographic endpoints missing data were imputed by means of linear extrapolation. In order to assess the robustness of results additional analyses using an LOCF approach or complete data only were performed.

Results

Participant flow

Of the 1846 patients screened 1162 patients were randomised to treatment. Five patients withdrew prior to receiving any study treatment.

Figure 15. Overview of 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).

The number of patients who completed Week 24 and Week 52 (87%-89% and 79%-81%, respectively) was similar across treatment groups.

The rate of withdrawal was calculated at Week 24 of the study, which was the time point at which the primary endpoint was evaluated and at Week 52. The proportion of patients who prematurely withdrew from treatment was balanced between the four treatment groups at Week 24 (ranging from 11% – 13% of patients) and Week 52 (19% – 22% of patients). However, there was an imbalance in the proportion of patients who withdrew for safety/non-safety reasons between treatment groups at both Week 24 and Week 52.

At Week 24, in the placebo + MTX group, withdrawals were mainly driven by non–safety-related reasons versus safety reasons (27 versus 5 patients), most notably insufficient therapeutic response and refused treatment. Whereas, in the TCZ 8mg/kg + MTX treatment group, the withdrawal rates were driven chiefly by safety reasons versus non–safety-related reasons (29 versus 11 patients), mostly AEs.

Withdrawals were evenly split between safety and non-safety related reasons in the TCZ 4 mg/kg + MTX (17 versus 18 patients) and TCZ 8 mg/kg monotherapy treatment group (15 patients versus 17 patients).

Recruitment

The first patient was screened on 30 September 2009, and the first patient was enrolled on 19 October 2009. The last patient was enrolled on 17 May 2011 and the last patient completed Week 52 on 23 May 2012.

Conduct of the study

There were two substantial amendments to the original study protocol:

- Amendment B (14 December 2009): Changes in the study protocol included:

  - Implementation of the dose capping strategy in which patients weighing > 100 kg had their TCZ/placebo dose capped at 800 mg.
  - Update of the risk mitigation strategy.
- Amendment C (7 January 2011): Major change was the introduction of additional guidance on how to proceed in case of anaphylaxis or serious hypersensitivity.

Baseline data

Table 12. Summary of baseline demographic characteristics (ITT population)

stdm11_gen_itt Summary of Patient Demographics (ITT Population) Protocol(s): R19926A
Analysis: INTENT TO TREAT Center: ALL CENTERS

	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
Sex				
MALE	58 (20%)	60 (21%)	62 (21%)	73(25%
FEMALE	229 (80%)	228 (79%)	228 (79%)	219(75%
n	287	288	290	292
Race				
AMERICAN INDIAN OR ALASKA NATIVE	3 (1%)	7 (2%)	4 (1%)	6(2%
ASIAN	22 (8%)	25 (9%)	18 (6%)	24(8%
BLACK	11 (4%)	7 (2%)	6 (2%)	10(3%
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	2 (<1%)	-	-	-
OTHER	28 (10%)	31 (11%)	33 (11%)	31(11%
WHITE	221 (77%)	218 (76%)	229 (79%)	221(76%
n	287	288	290	292
Age in years				
Mean	49.6	51.2	49.5	49.9
SD	13.10	13.84	13.70	13.22
SEM	0.77	0.82	0.80	0.77
Median	50.0	53.0	50.5	51.0
Min-Max	19 - 82	18 - 83	18 - 79	18 - 84
n	287	288	290	292
Weight in kg				
Mean	74.14	73.90	74.82	75.02
SD	19.818	18.946	19.278	17.533
SEM	1.170	1.116	1.132	1.026
Median	71.00	70.50	72.00	73.10
Min-Max	37.4 - 167.3	36.7 - 160.4	42.0 - 150.0	43.0 -152.7
Height in cm				
Mean	164.0	163.1	163.5	164.3
SD	9.60	9.86	10.24	9.93
SEM	0.57	0.58	0.60	0.58
Median	163.0	161.0	164.0	164.0
Min-Max	140 - 193	142 - 193	120 - 201	132 - 192
n	285	286	290	292
Ethnicity				
HISPANIC	50 (17%)	69 (24%)	64 (22%)	66 (23%
NON-HISPANIC	237 (83%)	219 (76%)	226 (78%)	225 (77%
n	287	288	290	291
Geographic Region				
EUROPE	93 (32%)	94 (33%)	93 (32%)	93 (32%
NORTH AMERICA	92 (32%)	93 (32%)	94 (32%)	95 (33%
REST OF WORLD	60 (21%)	59 (20%)	60 (21%)	61 (21%
SOUTH AMERICA	42 (15%)	42 (15%)	43 (15%)	43 (15%
n	287	288	290	292
Female reproductive status				
POSTMENOPAUSAL	96 (42%)	103 (45%)	85 (37%)	98 (45%
SURGICALLY STERIL.	40 (17%)	41 (18%)	45 (20%)	34 (16%
WITH CONT. PROT.	91 (40%)	81 (36%)	97 (43%)	79 (36%
WITHOUT CONT. PROT.	2 (<1%)	3 (1%)	1 (<1%)	8 (4%
n	229	228	228	219
Body Mass Index (kg/m2)				
Mean	27.50	27.74	27.97	27.80
SD	6.564	6.515	6.957	5.938
SEM	0.389	0.385	0.409	0.348
Median	26.40	26.80	26.60	27.25
Min-Max	13.6 - 63.0	11.5 - 53.8	16.3 - 68.8	15.6 - 46.8
n	285	286	290	292

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
For reproductive status, Cont. Prot. stands for Contraceptive Protection.
DM11 15AUG2012:15:50:16

Table 13. Summary of RA baseline disease characteristics (ITT population)

	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
Duration of RA (years)				
Mean	0.4	0.4	0.5	0.5
SD	0.48	0.49	0.53	0.48
SEM	0.03	0.03	0.03	0.03
Median	0.2	0.2	0.3	0.2
Min-Max	0 - 2	0 - 2	0 - 2	0 - 2
n	287	288	290	292
No. of previous DMARDS				
Mean	0.2	0.2	0.2	0.3
SD	0.41	0.41	0.49	0.52
SEM	0.02	0.02	0.03	0.03
Median	0.0	0.0	0.0	0.0
Min-Max	0 - 2	0 - 2	0 - 3	0 - 3
n	287	288	290	292
Oral Corticosteroid Use (y/n)				
NO	178 (62%)	181 (63%)	195 (67%)	174 (60%)
YES	109 (38%)	107 (37%)	95 (33%)	118 (40%)
n	287	288	290	292
Baseline Rheumatoid Factor				
NEGATIVE	33 (11%)	33 (11%)	26 (9%)	29 (10%)
POSITIVE	254 (89%)	255 (89%)	264 (91%)	262 (90%)
n	287	288	290	291
Baseline Anti-CCP antibody				
NEGATIVE	41 (14%)	41 (14%)	38 (13%)	41 (14%)
POSITIVE	246 (86%)	245 (86%)	252 (87%)	247 (86%)
n	287	286	290	288
Baseline DAS28 Score				
Mean	6.6	6.7	6.7	6.7
SD	0.99	1.05	1.11	0.99
SEM	0.06	0.06	0.06	0.06
Median	6.5	6.7	6.8	6.7
Min-Max	3 - 9	4 - 9	3 - 9	4 - 9
n	287	288	290	292

The study was designed to recruit patients with RA duration of ≤ 2 years. The mean and median duration of RA across treatment groups was 0.4−0.5 years and 0.2−0.3 years, respectively.

RF and anti-CCP Ab positivity was a stratification factor for randomisation and RF and anti-CCP Ab negativity was limited to 20%. Thus the majority of patients in all treatment groups (89%−91% and 86%−87%, respectively) were positive for RF and anti-CCP Ab at baseline.

In all four treatment groups, the mean DAS28 at baseline was high at 6.6−6.7 (range: 3.0−9.0), reflecting the severity of disease in the recruited early RA patient population (severe disease being defined as a DAS28 > 5.1).

The number of previously used DMARDs was low (mean, 0.2−0.3) across all treatment groups. In fact, the majority of patients (76.4%−81.7% across all treatment groups) were also DMARD-naïve.

The percentage of patients using oral corticosteroids was also relatively low across all treatment groups but slightly fewer patients in the TCZ 8 mg/kg + MTX group were using oral corticosteroids at baseline compared with the other three treatment groups (33% versus 37% [TCZ 4 mg/kg + MTX], 40% [TCZ 8 mg/kg + placebo], and 38% [placebo + MTX]).

Other baseline disease characteristics (including SJC66, TJC68, ESR, CRP, HAQ-DI, Pain VAS, physician VAS and Global VAS score) were generally balanced between all four treatment groups and the number of active joints, elevated ESR or CRP, high HAQ-DI and VAS scores again indicated that the RA population recruited had active, progressive disease. The mean and median values of DAS28 components were balanced across treatment groups.

Numbers analysed

The primary analysis population for efficacy was the intent-to-treat (ITT) population, which comprises all patients randomized into the study, provided at least one TCZ/placebo infusion was administered.

Table 14. Populations by Randomized Trial Treatment (All Patients Population)

	PLACEBO + MTX	TCZ 4 MG/KG + MTX	TCZ 8 MG/KG + MTX	TCZ 8 MG/KG + PLACEBO
No. of Patients Randomized	289	290	291	292
No. Included in INTENT TO TREAT	287	288	290	292
No. Excluded from INTENT TO TREAT	2	2	1	-
RECEIVED NO INFUSION OF I.V. STUDY TREATMENT (TCZ/PLACEBO) UP TO WEEK 24	2	2	1	-

Outcomes and estimation

Table 15. Primary efficacy endpoint and secondary endpoints presented as per hierarchical testing

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

Order	Endpoint	TCZ Dose (mg/kg) Compared with Placebo + MTX	p-value (Hierarchy)
14	Proportion of patients with ACR50 response at Week 24	8 (monotherapy)	0.2743 (NS)
15	Proportion of patients with ACR70 response at Week 24	8 (monotherapy)	0.1954 (NS)
16	Change from baseline in mTSS at Week 52	8 (monotherapy)	0.0004
17	Change from baseline in modified Sharp erosion score at Week 52	8 (monotherapy)	<0.0001
18	Proportion of patients with a DAS28 remission response (DAS28 < 2.6) at Week 24	4 + MTX	<0.0001
19	Proportion of patients with ACR50 response at Week 24	4 + MTX	0.2419 (NS)
20	Proportion of patients with ACR70 response at Week 24	4 + MTX	0.0138
21	Change from baseline in mTSS at Week 52	4 + MTX	0.0051
22	Change from baseline in modified Sharp erosion score at Week 52	4 + MTX	0.0117
23	Proportion of patients with ACR20 response at Week 24	8 (monotherapy)	0.1830 (NS)
24	Proportion of patients with a DAS28 remission response (DAS28 < 2.6) at Week 52	8 (monotherapy)	<0.0001
25	Proportion of patients with ACR50 response at Week 52	8 (monotherapy)	0.0358
26	Proportion of patients with ACR70 response at Week 52	8 (monotherapy)	0.0630 (NS)
27	Proportion of patients with ACR20 response at Week 52	8 (monotherapy)	0.1406 (NS)
28	Change from baseline in HAQ-DI score at Week 52	8 (monotherapy)	0.5532 (NS)
29	Change from baseline in HAQ-DI score at Week 24	8 (monotherapy)	0.4546 (NS)
30	Proportion of patients with ACR20 response at Week 24	4 + MTX	0.0249
31	Proportion of patients with a DAS28 remission response (DAS28 < 2.6) at Week 52	4 + MTX	<0.0001

Order	Endpoint	TCZ Dose (mg/kg) Compared with Placebo + MTX	p-value (Hierarchy)
32	Proportion of patients with ACR50 response at Week 52	4 + MTX	0.0045
33	Proportion of patients with ACR70 response at Week 52	4 + MTX	0.0315
34	Proportion of patients with ACR20 response at Week 52	4 + MTX	0.1511 (NS)
35	Change from baseline in HAQ-DI score at Week 52	4 + MTX	0.0515 (NS)
36	Change from baseline in HAQ-DI score at Week 24	4 + MTX	0.0490
37	Major clinical response (defined as achieving a continuous six-month period of success by the ACR70) at Week 52	8 + MTX	<0.0001
38	Change from baseline in modified Sharp JSN score at Week 52	8 + MTX	0.0008
39	Major clinical response at Week 52	8 (monotherapy)	0.1005 (NS)
40	Change from baseline in modified Sharp JSN score at Week 52	8 (monotherapy)	0.0123
41	Major clinical response at Week 52	4 + MTX	0.0681 (NS)
42	Change from baseline in modified Sharp JSN score at Week 52	4 + MTX	0.0331
43	Change from baseline in SF-36 Physical Component score at Week 24	8 + MTX	0.0014
44	Change from baseline in SF-36 Physical Component score at Week 52	8 + MTX	0.0066
45	Change from baseline in SF-36 Physical Component score at Week 24	8 (monotherapy)	0.5282 (NS)
46	Change from baseline in SF-36 Physical Component score at Week 52	8 (monotherapy)	0.8489 (NS)
47	Change from baseline in SF-36 Physical Component score at Week 24	4 + MTX	0.0914 (NS)
48	Change from baseline in SF-36 Physical Component score at Week 52	4 + MTX	0.2503 (NS)

Note: Hierarchical chain broke at #14; comparisons that fell after the chain break are highlighted grey.

Primary endpoint

The study met its primary endpoint of proportion of patients with DAS28 remission (DAS< 2.6).

The proportion of patients in DAS28 remission at Week 24 was significantly higher in the TCZ 8 mg/kg + MTX group than in the placebo + MTX group (44.8% versus 15.0%; OR = 4.77, 95%-CI: 3.19 – 7.14; p < 0.0001).

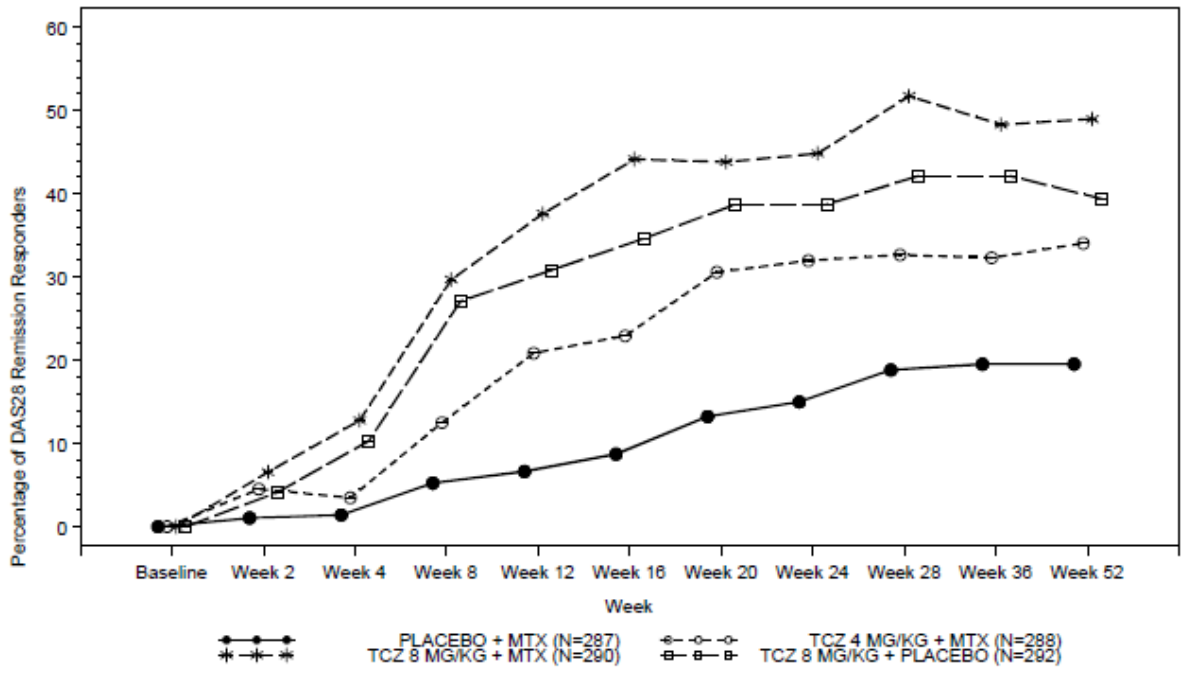
The proportion of patients in DAS28 remission at Week 24 was also significantly higher in the TCZ 8 mg/kg + placebo group than in the placebo + MTX group (38.7% versus 15.0%; OR = 3.70; 95%-CI: 2.47 – 5.55; p < 0.0001). The proportion of patients in DAS28 remission in the TCZ 4 mg/kg + MTX was numerically greater than in the placebo + MTX group (31.9% versus 15.0%; OR = 2.72; 95%-CI: 1.80 – 4.11) however, this comparison fell after the hierarchical break in statistical testing.

The two robustness analyses performed (observed case and LOCF analysis) showed results consistent with the logistic regression analysis. In addition, an analysis using the Cochran-Mantel-Haenszel test adjusted for the stratification variables of region and serologic status showed that a higher proportion of patients who achieved DAS28 remission in the TCZ treatment group (44.8% [TCZ 8 mg/kg + MTX], 38.7% [TCZ 8 mg/kg + placebo] and 31.9% [TCZ 4 mg/kg + MTX]) compared with 15% [placebo + MTX], which is consistent with the logistic regression results.

Secondary and exploratory endpoints

DAS28 Remission over Time

Figure 16. Percentage of Patients with DAS28 Remission Status by Visit (ITT Population)



A clear separation between TCZ 8 mg/kg + MTX and TCZ 8 mg/kg + placebo compared with the placebo + MTX group was apparent by Week 4, with the percentage of patients achieving DAS28 remission being 12.8% [TCZ 8 mg/kg + MTX] and 10.3% [TCZ 8 mg/kg + placebo] compared with 1.4% in the placebo + MTX group.

A clear separation between TCZ 4 mg/kg + MTX and placebo + MTX group was apparent by Week 8, with the percentage of patients achieving DAS28 remission being 12.5% in TCZ 4 mg/kg + MTX group compared with 5.2% in the placebo + MTX group.

To assess the maintenance of the effect of the DAS28 remission, an exploratory analysis of the proportion of DAS28 remission responders at both Weeks 24 and 52 was performed. This showed that 79.2% of Week 24 responders were still a DAS28 responder at Week 52 in the TCZ 8 mg/kg + MTX group compared with 55.8% in the placebo + MTX group. In all, 70.8% of patients in the TCZ 8 mg/kg

+ placebo group maintained their response from Week 24 to Week 52 as did 76.1% of patients in the TCZ 4 mg/kg + MTX group.

Table 16. Shift Table of Proportion of DAS28 Remission Responders at Weeks 24 and 52 (ITT Population)

	Week 52		
Week 24	Non-Responder	Responder	Total
PLACEBO + MTX (N = 287)			
Non-Responder	212 (86.9%)	32 (13.1%)	244
Responder	19 (44.2%)	24 (55.8%)	43
Total	231	56	287
TCZ 4 MG/KG + MTX (N = 288)			
Non-Responder	168 (85.7%)	28 (14.3%)	196
Responder	22 (23.9%)	70 (76.1%)	92
Total	190	98	288
TCZ 8 MG/KG + MTX (N = 290)			
Non-Responder	121 (75.6%)	39 (24.4%)	160
Responder	27 (20.8%)	103 (79.2%)	130
Total	148	142	290
TCZ 8 MG/KG + PLACEBO (N = 292)			
Non-Responder	144 (80.4%)	35 (19.6%)	179
Responder	33 (29.2%)	80 (70.8%)	113
Total	177	115	292

LOCF used for tender and swollen joint counts, no imputation used for ESR and Patient's Global Assessment of Disease Activity VAS
If ESR=0 then ESR=1 is substituted into the DAS28 calculation to enable a non-missing DAS28.
Patients who withdrew prematurely or where a DAS28 could not be calculated, have been set to 'Non Responder'.
Remission: DAS28 < 2.6

Table 17. Patients with DAS28 Remission Responses at Week 24 by Week 24 C_{min} Quartiles – Study WA19926

	TCZ 4 or 8 mg/kg + MTX [a]				**TCZ 8 mg/kg + MTX**				**TCZ 8 mg/kg + Placebo**			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Number of patients	155	94[b]	124	124	63	63	64	61	65	64	64	64
Mean C_{min} (µg/mL)	0.0	0.58	8.01	26.8	2.15	10.5	18.4	35.4	2.41	10.4	19.0	39.7
Median C_{min} (µg/mL)	0.0	0.31	8.15	23.8	1.18	10.2	18.4	30.7	1.98	10.9	18.7	31.0
DAS28 responders, n (%)	50 (32)	34 (36)	60 (48)	73 (59)	24 (38)	30 (48)	41 (64)	33 (54)	25 (39)	27 (42)	30 (47)	29 (45)

[a] Includes all patients from 4mg/kg TCZ + MTX and 8mg/kg TCZ + MTX groups combined.
[b] There was a slight imbalance in the first and second quartiles of this "combination" group, since a total of 155 patients had unmeasurable concentrations; this was largely a consequence of the low trough concentrations seen with TCZ 4 mg/kg dosing. See Section 2.3.2 of the Summary of Clinical Pharmacology for further details.
Q1-Q4 refer to the subgroups by C_{min} exposure quartile (from lowest to highest C_{min}).
Remission: DAS28 < 2.6

DAS28 Low Disease Activity (≤ 3.2)

The proportion of patients achieving DAS28 low disease activity at Week 24 was numerically higher in TCZ treatment groups compared with placebo + MTX treatment group (57.6% [TCZ 8 mg/kg + MTX], 50.7% [TCZ 8 mg/kg + placebo], 45.5% [TCZ 4 mg/kg + MTX], and 26.8% [placebo + MTX]), respectively, with the highest proportion of responders in the TCZ 8 mg/kg + MTX group. The results at Week 52 were similar to those seen at Week 24.

ACR20, ACR50, ACR70

The response rates were numerically higher for all TCZ groups in comparison with placebo + MTX, with the highest response rates seen in the TCZ 8 mg/kg + MTX group. Similar results were seen at Week 52.

Table 18. ACR20/50/70 at Week 24 (ITT population)

	WA19926			
	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**
ACR20 responders, n (%)	187 (65.2)	212 (73.6)[b]	216 (74.5)[c]	205 (70.2)
Weighted difference vs. MTX (95%CI)		0.09 (0.01, 0.16)	0.09 (0.02, 0.17)	0.05 (-0.02, 0.13)
ACR50 responders, n (%)	124 (43.2)	138 (47.9)	165 (56.9)[c]	139 (47.6)
Weighted difference vs. MTX (95%CI)		0.05 (-0.03, 0.13)	0.14 (0.06, 0.22)	0.05 (-0.03, 0.13)
ACR70 responders, n (%)	73 (25.4)	100 (34.7)[b]	112 (38.6)[c]	88 (30.1)
Weighted difference vs. MTX (95%CI)		0.09 (0.02, 0.17)	0.13 (0.06, 0.21)	0.05 (-0.02, 0.12)

ITT = intent-to-treat population, RA = rheumatoid arthritis, MTX = methotrexate

[a] Patients in WA17824 who had ≤2 years RA at baseline

[b] $p < 0.05$; however, this comparison occurred after the break in hierarchical ordered testing sequence.

[c] $p < 0.05$.

Table 19. Shift Table of Proportion of ACR20 Responders at Weeks 24 and 52 (ITT Population)

Week 24	Week 52 Non-Responder	Responder	Total
PLACEBO + MTX (N = 287)			
Non-Responder	76 (76.0%)	24 (24.0%)	100
Responder	47 (25.1%)	140 (74.9%)	187
Total	123	164	287
TCZ 4 MG/KG + MTX (N = 288)			
Non-Responder	60 (78.9%)	16 (21.1%)	76
Responder	47 (22.2%)	165 (77.8%)	212
Total	107	181	288
TCZ 8 MG/KG + MTX (N = 290)			
Non-Responder	58 (78.4%)	16 (21.6%)	74
Responder	37 (17.1%)	179 (82.9%)	216
Total	95	195	290
TCZ 8 MG/KG + PLACEBO (N = 292)			
Non-Responder	60 (69.0%)	27 (31.0%)	87
Responder	48 (23.4%)	157 (76.6%)	205
Total	108	184	292

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

Exploratory analysis of the proportion of ACR20 responders at both Weeks 24 and 52 simultaneously showed that high proportions of patients maintained an ACR20 response from Week 24 to Week 52 in all treatment groups. The results also showed that the TCZ treatment groups achieved a higher proportion of patients who maintained ACR20 response from Week 24 to Week 52 compared with placebo + MTX (82.9% [TCZ 8 mg/kg + MTX], 76.6% [TCZ 8 mg/kg + placebo], 77.8% [TCZ 4 mg/kg + MTX] and 74.9% [placebo + MTX]). In addition, this summary showed that a number of patients achieved a late ACR20 response given that approximately 20% of the Week 24 non-responders went on to achieve an ACR20 response at Week 52 in the TCZ 8 mg/kg + MTX, TCZ 4 mg/kg + MTX, and placebo + MTX groups. In the TCZ 8 mg/kg + placebo group, 31% of Week 24 non-responders achieved an ACR20 response at Week 52.

Major Clinical Response

A major clinical response (MCR) was defined as maintenance of an ACR70 response for a continuous period of 24 weeks (or longer). The percentage of patients who achieved a MCR by Week 52 was numerically higher for TCZ treatment groups compared with placebo + MTX (31% [TCZ 8 mg/kg + MTX], 22% [TCZ 8 mg/kg + placebo], 22% [TCZ 4 mg/kg + MTX] and 16% [placebo + MTX]).

These findings were consistent with the results observed for ACR20 and ACR50 up to Week 52. Both endpoints also showed numerically higher percentages of patients maintaining a response for at least 24 weeks continuously in the TCZ 8 mg/kg + MTX (66% ACR20; 46% ACR50); TCZ 8 mg/kg + placebo (59% ACR20; 38% ACR50); and TCZ 4 mg/kg + MTX (57% ACR20; 40% ACR50) when compared with placebo + MTX (50% ACR20; 32% ACR50), although they were not evaluated statistically.

Modified Total Sharp-van de Heijde Score (mTSS)

The mean change from baseline to Week 52 in mTSS was significantly lower in the TCZ 8mg/kg + MTX group compared with placebo + MTX (0.08 versus1.14; p = 0.0001). Numerically lower mean changes from baseline to Week 52 in mTSS were also observed for the TCZ 8 mg/kg + placebo and TCZ 4 mg/kg + MTX groups versus placebo + MTX(0.26 and 0.42 versus 1.14, respectively). The percentage

reductions in mTSS (from baseline to Week 52) compared with placebo + MTX were 93% [TCZ 8 mg/kg + MTX], 77% [TCZ 8 mg/kg + placebo], and 63% [TCZ 4 mg/kg + MTX].

Modified Sharp Erosion Score

The mean change from baseline to Week 52 in modified Sharp erosion score was significantly lower in TCZ 8 mg/kg + MTX treatment group compared with placebo + MTX (0.05 versus 0.63, respectively; p = 0.00069). Numerically lower mean change from baseline to Week 52 in mTSS was observed for TCZ 8 mg/kg + placebo and TCZ4 mg/kg + MTX groups compared with placebo + MTX group (0.15 and 0.25 versus 0.63).

Modified Joint Space Narrowing

The mean change from baseline to Week 52 in JSN was numerically lower for all TCZ groups compared with placebo + MTX (0.03 [TCZ 8 mg/kg + MTX], 0.11 [TCZ 8 mg/kg + placebo], 0.17 [TCZ 4 mg/kg + MTX], and 0.51 [placebo + MTX].

Proportion of Patients without Radiographic Progression (Exploratory)

No progression (i.e., no worsening) was defined as a change from baseline of ≤ 0.

At Week 52, the proportion of patients with no progression from baseline in their total Sharp-van der Heijde score was greater in the TCZ treatment groups (83% [TCZ 8 mg/kg + MTX], 82% [TCZ 8 mg/kg + placebo and 79% [TCZ 4 mg/kg + MTX]) compared with 73% in the placebo + MTX group, with similar results at Week 24. The differences between the TCZ 8 mg/kg + MTX and TCZ 8 mg/kg + placebo groups compared with the placebo + MTX group yielded descriptive p-values <0.05 from the logistic regression stratified by region and serologic status at both Weeks 24 and 52; however, the comparison of TCZ 4 mg/kg + MTX and placebo + MTX did not yield a descriptive p<0.05.

At Week 52, the proportion of patients with no progression of erosion from baseline was greater in the TCZ groups (86% [TCZ 8 mg/kg + MTX], 87% [TCZ 8 mg/kg + placebo] and 83% [TCZ 4 mg/kg + MTX] compared with 76% in the placebo + MTX group). Similar results were observed at Week 24. The differences in the proportion of patients between both TCZ 8 mg/kg + MTX and TCZ 8 mg/kg + placebo groups compared with the placebo + MTX group yielded descriptive p-values <0.05 at both Weeks 24 and 52. The comparison of TCZ 4 mg/kg + MTX with placebo + MTX yielded a descriptive p-value <0.05 at Week 24 but did not at Week 52.

At Week 52, the proportion of patients with no progression of JSN from baseline was greater in the TCZ groups compared with placebo + MTX (93% [TCZ 8 mg/kg + MTX], 92% [TCZ 8 mg/kg + placebo], 91% [TCZ 4 mg/kg + MTX], and 88% [placebo + MTX] group). Similar results were seen at Week 24. The differences between the TCZ 8 mg/kg + MTX compared with placebo + MTX yielded descriptive p-values <0.05 at both Weeks 24 and 52. However, the comparisons of TCZ 8 mg/kg + placebo and TCZ 4 mg/kg + MTX groups with placebo + MTX for the proportion of patients with no JSN progression did not achieve descriptive p-values of < 0.05 at either timepoint.

ACR/EULAR Boolean and Index remission as well as CDAI remission (exploratory)

Since the initiation of the WA19926 study, ACR and EULAR have introduced more stringent remission measures, and therefore ACR/EULAR Boolean and Index remission as well as CDAI remission were added as exploratory endpoints in WA19926.

Table 20. Percentage of Patients with ACR/EULAR Remission (Boolean and Index-Based Definitions) at Weeks 24 and 52

	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
Week 24				
Boolean Remission	25/250	43/257	47/256	38/267
	10.0 %	16.7 %*	18.4 %*	14.2 %
Index Remission	41/250	58/257	73/256	60/266
	16.4 %	22.6 %	28.5 %*	22.6 %
Week 52				
Boolean Remission	34/219	48/228	59/230	43/230
	15.5 %	21.1%	25.7 %*	18.7 %
Index Remission	49/219	66/225	83/230	69/230
	22.4 %	29.3 %	36.1 %*	30.0 %

No imputation used for missing data

*Statistically significant, p<0.05 vs. Placebo + MTX (pre-specified exploratory endpoint, unadjusted for multiplicity)

The remission rate was greater in all three TCZ treatment groups than in the placebo + MTX group, across all remission endpoints. At Week 24, a greater proportion of patients achieved the most stringent ACR/EULAR Boolean remission in both the TCZ 8 mg/kg and 4 mg/kg + MTX treatment groups compared to the placebo + MTX group (descriptive p-value 0.0095 and 0.0287, respectively).

Additionally, the TCZ 8 mg/kg + MTX treatment group had a greater proportion of patients achieving ACR/EULAR Index remission compared to placebo + MTX at Week 24 (descriptive p-value 0.0013).

Table 21. Percentage of Patients with CDAI Remission at Weeks 24 and 52

	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
Week 24				
CDAI Remission	13.2 %	22.2 %	24.5 %	20.5 %
p-value		0.0041	0.0005	0.0153
Week 52				
CDAI Remission	19.9 %	25.0 %	32.1 %	24.0 %
p-value		0.1338	0.0006	0.2015

Remission is CDAI ≤ 2.8.

p-values are exploratory and not adjusted for multiplicity.

All comparisons are to placebo + MTX.

Cochran-Mantel-Haenszel analysis stratified by region and serologic status was used to calculate p-values to compare remission rates.

Data collected after withdrawal is set to missing. LOCF used for missing data.

The analysis of remission by CDAI, which does not include markers of inflammation, CRP and ESR, shows that the higher remission response rates for TCZ therapy compared to MTX alone are robust and not greatly influenced by acute phase reactants. The exploratory analysis of the proportion of patients

in CDAI remission at Week 24, found that a greater proportion achieved remission in all TCZ treatment groups compared with placebo + MTX (descriptive p-values <0.05).

Preliminary Week 104 results from study WA19926

The preliminary Week 104 results for study WA19926 have been provided.

Table 22. WA19926 Key Efficacy Parameters at Week 104

		Placebo + MTX N=287	TCZ 4 mg/kg + MTX N=288	TCZ 8 mg/kg + MTX N=290
DAS28 Remission Responders (No. of Patients [%])				
DAS28 Remission (DAS28 < 2.6)	Wk 104	46 [16.0]	81 [28.1]	138 [47.6]
ACR Responders (No. of Patients [%])				
ACR20 [a]	Wk 104	73 [25.4]	114 [39.6]	189 [65.2]
ACR50 [a]	Wk 104	63 [22.0]	105 [36.5]	167 [57.6]
ACR70 [a]	Wk 104	50 [17.4]	91 [31.6]	135 [46.6]
Radiographic Endpoints (Campaign 2)				
mTSS LE (Mean change from BL [SD]) [a]	Wk 52	0.97 [3.21]	0.75 [5.90]*	0.13 [1.28]
	Wk 104	1.88 [6.24]	1.43 [11.67]*	0.19 [2.08]
mTSS Observed (Mean change from BL [SD]) [b]	Wk 52	0.91 [2.81]	0.34 [1.71]	0.10 [0.94]
	Wk 104	0.57 [1.34]	0.39 [1.46]	0.05 [1.27]
Annualized Progression Rate for mTSS (mean [SD])	BL to Wk 52	0.87 [2.71]	0.33 [1.62]	0.09 [0.89]
	Wk 52 to 104	0.23 [0.76]	0.12 [0.81]	0.00 [0.62]
HAQ-DI				
HAQ-DI ≥ 0.3 Response [b]	n	80	120	205
	Wk 104	64 (80.0%)	103 (85.8%)	171 (83.4%)

BL: Baseline; mTSS: Modified total Sharp-van de Heijde score; Wk: Week; HAQ-DI: Health Assessment Questionnaire – Disability Index; LE: Linear extrapolation

145 patients in the placebo + MTX group and 193 patients in the TCZ 4 mg/kg + MTX group did not escape to TCZ 8 mg/kg + MTX at Week 52.

For DAS28 and ACR responses, an non-responder imputation was used- patients who received escape therapy, withdrew prematurely, or where a DAS28/ACR could not be calculated, were set to 'non-responder'.

[a] Missing data were imputed using linear extrapolation (LE).

[b] No imputation for missing data. Data collected after withdrawal and during escape are excluded.

* mTSS LE data for TCZ 4 mg/kg + MTX groups is believed to be skewed by data for one patient (205622/17567) whose data were imputed at Week 52 and Week 104 and are considerably higher than for all other patients in the group/study.

Source: WA19926 Week 104 outputs: eteprsp01_1_ndrv_ldarem, eteprsp06_1_ndrv_ldarem, eteprsp_1_ndrv_acrn2579, eteprsp05_1_ndrv_acrn2579, etexray01_1_ndrv_cmtssle_lf_c2, etexray_ah007_1_ndrv, etexray_1_ndrv_atss_xrwd_lf_c2, etefrsp02_1_v0

- Ninety-five of the 288 patients in the TCZ 4 mg/kg + MTX group escaped to TCZ 8 mg/kg + MTX at Week 52. These approximately 30% escape patients demonstrated that there was a substantial proportion of patients who did not achieve low disease activity at the lower TCZ dose after one year of treatment. After escape,

Ninety-five of the 288 patients in the TCZ 4 mg/kg + MTX group and 142 if the 287 patients in the Placebo + MTX group escaped to TCZ 8 mg/kg + MTX at Week 52.

Table 23. WA19926 Key Efficacy Parameters for Escape Patients at Week 104 (ITT)

		Placebo + MTX N=142	TCZ 4 mg/kg + MTX N=95
DAS28 Remission Responders (No. of Patients [%])			
DAS28 Remission (DAS28 < 2.6) [a]	Wk 52 RBL	73 [51.4]	29 [30.5]
ACR Responders (No. of Patients[%])			
ACR20 [a]	Wk 52 RBL	61 [43.0]	28 [29.5]
	Wk 104	105 [73.9]	63 [66.3]
ACR50 [a]	Wk 52 RBL	43 [30.3]	16 [16.8]
	Wk 104	85 [59.9]	50 [52.6]
ACR70 [a]	Wk 52 RBL	23 [16.2]	6 [6.3]
	Wk 104	65 [45.8]	31 [32.6]
Radiographic Endpoints (Campaign 2)			
mTSS Observed (Mean change from BL [SD])	Wk 52	1.49 [3.95]	0.68 [2.70]
	Wk 104	1.57 [4.56]	0.56 [2.63]
Annualized Progression Rate for mTSS Observed data, (mean [SD])	BL to Wk 52	1.43 [3.81]	0.65 [2.56]
	Wk 52 to 104	0.10 [1.16]	0.01 [0.69]

BL: Baseline; mTSS: Modified total Sharp-van de Heijde score; Wk: Week

RBL: Data were re-baselined at Week 52, Week 52 refers to 52 Weeks of escape treatment

[a] Patients who withdraw prematurely or where a response could not be calculated, were set to 'Non Responder'.

Source: WA19926 Week 104 outputs: eteprsp01_1_escp_le11_ldarem, eteprsp_1_escp_acrn2579, eteprsp03_1_escpt_acrn2579, etexray01_1_escpt_cmtss_xrwd_lf_c2, etexray_1_escpt_atss_xrwd_lf_c2

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24. Summary of Efficacy for trial WA19926

Title: A multi-centre, randomized, double-blind, parallel-group study of the 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.		
Study identifier	WA19926	
Design	A multi-centre, randomized, double-blind, parallel-group study	
	Duration of main phase:	104 weeks (results provided for week 52)
	Duration of run-in phase:	not applicable
	Duration of extension phase:	not applicable
Hypothesis	Superiority	

Treatment groups	TCZ 8mg/kg + MTX		TCZ 8 mg/kg every 4 weeks + MTX 7.5 – 20 mg weekly. Subjects randomised: 291
	TCZ 8 mg/kg + placebo		TCZ 8 mg/kg every 4 weeks + placebo. Subjects randomised: 292
	TCZ 4 mg/kg + MTX		TCZ 4 mg/kg every 4 weeks + MTX 7.5 – 20 mg weekly. Subjects randomised: 290
	Placebo +MTX		Placebo + MTX 7.5 – 20 mg weekly. Subjects randomised: 289
Endpoints and definitions	Primary endpoint	DAS28 W24	Proportion of patients with a Disease Activity Score of 28 joints remission response (DAS28 < 2.6) at week 24
	Secondary endpoint	DAS28 W52	Proportion of patients with a DAS28 remission response (DAS28 < 2.6) at week 52
	Secondary endpoint	ACR50 W24	Proportion of patients with ACR50[1] response at Week 24
	Secondary endpoint	mTSS W52	Change from baseline in modified total Sharp scores at week 52
Database lock	Cut-off for 52-week analysis: 23 May 2012		

Results and analysis

Analysis description	Primary analysis				
Analysis population and time point description	(Modified) intent to treat - All patients randomized into the study, providing at least one TCZ/placebo infusion was administered/taken. Analysis at week 24 or week 52 (as indicated)				
Descriptive statistics and estimate variability	Treatment group	TCZ 8mg/kg + MTX	TCZ 8 mg/kg + placebo	TCZ 4 mg/kg + MTX	Placebo +MTX
	Number of subjects	290	292	288	287
	DAS28 W24 (No. [%] of subjects)	130 (44.8)	113 (38.7)	92 (31.9)	43 (15.0)
	95% CI	39.1 – 50.6]	33.1 – 44.3	26.6 – 37.3	10.9 – 19.1
	DAS28 W52 (No. [%] of subjects)	142 (49.0)	115 (39.4)	98 (34.0)	56 (19.5)
	Variability statistic	not reported			
	ACR50 W24 (No. [%] of subjects)	165 (56.9)	139 (47.6)	138 (47.9)	124 (43.2)
	Variability statistic	not reported			
	mTSS W52 (mean)	0.08	0.26	0.42	1.14
	SD	2.090	1.876	2.929	4.297

Effect estimate per comparison	Comparison of the group vs. Placebo +MTX		TCZ 8mg/kg + MTX	TCZ 8 mg/kg + placebo	TCZ 4 mg/kg + MTX
	Primary endpoint	DAS28 W24 (Odds ratio)	4.77	3.70	2.72

[1] at least a 50% 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)

		95% CI	3.19 – 7.14	2.47 – 5.55	1.80 – 4.11
		P-value	< 0.0001	< 0.0001	< 0.0001
	Secon-dary endpoint	DAS28 W52 (Odds ratio)	4.18	2.79	2.19
		95% CI	2.86 – 6.10	1.91 – 4.09	1.49 – 3.23
		P-value	< 0.0001	< 0.0001	< 0.0001
	Secon-dary endpoint	ACR50 W24 (Odds ratio)	1.76	1.20	1.22
		95% CI	1.26 – 2.45	0.86 – 1.68	0.87 – 1.70
		P-value	0.0009	0.2743	0.2419
	Secon-dary endpoint	mTSS W52	0.08 vs. 1.14	0.26 vs. 1.14	0.42 vs. 1.14
		P-value	0.0001	0.0004	0.0051

Supportive studies

Study WA17824

Study WA17824 was a Phase III 24-week global study assessing the safety and efficacy of TCZ 8 mg/kg + placebo MTX versus MTX + placebo TCZ, in patients with active RA. Data from the primary analysis at Week 24 have been submitted previously.

Data from a subgroup of these patients with early RA (RA duration of ≤ 2 years at baseline, similar to the definition used in WA19926) were presented to provide supportive evidence of signs and symptoms efficacy in an early RA population.

Study MRA012JP

Study MRA012JP was conducted by co-development partner Chugai in Japan. It was designed to investigate whether TCZ (8 mg/kg) monotherapy provided radiographic and clinical benefit in patients with active RA who had an inadequate response to conventional DMARDs. Whilst conducted in a different patient population to the population studied in WA19926 (the median baseline duration of RA was 2 years in MRA012JP) this study provided supportive radiographic evidence of the efficacy of TCZ monotherapy.

Study WA17823

Study WA17823 was Phase III study assessing the safety and prevention of structural joint damage during treatment with TCZ (8mg/kg or 4 mg/kg) + MTX versus placebo + MTX in patients with moderate to severe active RA who had an inadequate response to MTX (MTX-IR). Data from study WA17823 were assessed previously. In the current submission LTE data are summarised.

Baseline characteristics

Table 25. Baseline Characteristics and Rheumatoid Arthritis Disease History in WA19926, WA17824 and WA17824 (ITT)

	WA19926				WA17824 Complete ITT		WA17824 Early RA ITT[a]	
	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	Placebo + MTX N=284	TCZ 8 mg/kg + Placebo N=286	Placebo + MTX N=125	TCZ 8 mg/kg + Placebo N=116
Duration of RA, in years								
n	287	288	290	292	284	286	125	116
Mean (SD)	0.4 (0.48)	0.4 (0.49)	0.5 (0.53)	0.5 (0.48)	6.2 (7.81)	6.4 (7.93)	0.7 (0.45)	0.7 (0.47)
Median (range)	0.2 (0, 2)	0.2 (0, 2)	0.3 (0, 2)	0.2 (0, 2)	3.1 (0, 50)	3.1 (0, 45)	0.5 (0, 2)	0.6 (0, 2)
MTX-naïve								
n	287	288	290	292	284	286	125	116
No	0	0	0	0	94 (33%)	95 (33%)	15 (12%)	11 (9%)
Yes	287 (100%)	288 (100%)	290 (100%)	292 (100%)	190 (67%)	191 (67%)	110 (88%)	105 (91%)
DAS28 score								
n	287	288	290	292	282	284	123	115
Mean (SD)	6.6 (0.99)	6.7 (1.05)	6.7 (1.11)	6.7 (0.99)	6.8 (0.89)	6.8 (1.01)	6.8 (0.85)	6.6 (1.01)
Median (range)	6.5 (3, 9)	6.7 (4, 9)	6.8 (3, 9)	6.7 (4, 9)	6.8 (4, 9)	6.8 (4, 9)	6.8 (5, 9)	6.6 (4, 9)
Baseline RF								
n	287	288	290	291	284	286	125	116
Negative	33 (11%)	33 (11%)	26 (9%)	29 (10%)	72 (25%)	73 (26%)	38 (30%)	36 (31%)
Positive	254 (89%)	255 (89%)	264 (91%)	262 (90%)	212 (75%)	213 (74%)	87 (70%)	80 (69%)
Oral steroid use								
n	287	288	290	292	284	286	125	116
No	178 (62%)	181 (63%)	195 (67%)	174 (60%)	151 (53%)	149 (52%)	72 (58%)	64 (55%)
Yes	109 (38%)	107 (37%)	95 (33%)	118 (40%)	133 (47%)	137 (48%)	53 (42%)	52 (45%)
No. prior DMARDS								
n	287	288	290	292	284	286	284	286
Mean (SD)	0.2 (0.41)	0.2 (0.41)	0.2 (0.49)	0.3 (0.52)	1.1 (1.43[b]	1.2 (1.34)[b]	1250.4 (0.8)[b]	1160.4 (0.7)[b]
Median (range)	0.0 (0-2)	0.0 (0-2)	0.0 (0-3)	0.0 (0-3)	1.0 (0-7)	1.0 (0-7)	0.0 (0-5)	0.0 (0-3)
TJC (68 joints)								
n	287	288	290	292	284	286	125	116
Mean (SD)	27.4 (16.54)	28.1 (15.63)	28.7 (16.74)	28.7 (16.33)	31.1 (14.09)	31.8 (14.82)	30.9 (13.56)	30.0 (13.93)
Median (range)	23.0 (4, 68)	25.0 (6, 68)	24.5 (2, 68)	25.0 (6, 68)	30.5 (9, 68)	31.0 (8, 68)	31.0 (9, 64)	30.0 (8, 63)
SJC (66 joints)								
n	287	288	290	292	284	286	125	116
Mean (SD)	16.2 (10.44)	16.1 (10.16)	17.6 (12.38)	16.5 (10.10)	19.2 (10.55)	19.1 (11.01)	19.8 (9.72)	18.6 (10.74)
Median (range)	13.0 (4, 65)	13.0 (2, 61)	14.0 (0, 66)	13.0 (4, 62)	17.0 (6, 66)	16.5 (6, 65)	18.0 (6, 52)	16.0 (6, 56)
CRP (mg/dL)								
n	287	288	290	292	284	286	125	116
Mean (SD)	2.31 (2.67)	2.59 (3.05)	2.58 (2.98)	2.48 (3.19)	3.07 (3.39)	2.96 (3.27)	3.62 (4.07)	3.27 (3.56)
Median (range)	1.28 (0, 13)	1.58 (0.0, 21)	1.69 (0.0, 22)	1.26 (0, 21)	2.11 (0, 23)	1.76 (0, 18)	2.21 (0, 23)	1.91 (0, 18)
HAQ-DI								
n	284	287	286	289	283	285	124	116
Mean (SD)	1.48 (0.66)	1.62 (0.66)	1.50 (0.62)	1.58 (0.67)	1.5 (0.63)	1.6 (0.66)	1.5 (0.64)	1.5 (0.67)
Median (range)	1.50 (0.0, 3.0)	1.75 (0.0, 3.0)	1.50 (0.0, 3.0)	1.63 (0.0, 3.0)	1.6 (0, 3)	1.6 (0, 3)	1.6 (0, 3)	1.5 (0, 3)

CRP = C-reactive protein, DMARD = disease-modifying antirheumatic drug, ITT = intent-to-treat population, RA = rheumatoid arthritis, RF = rheumatoid factor, MTX = methotrexate, SD = standard deviation, SJC = swollen joint count, TJC = tender joint count

[a] Patients in WA17824 who had ≤2 years RA at baseline. [b] For WA17824, prior DMARDs includes prior anti-TNF agents.

Comparison of Study WA19926 and MRA012JP

While study MRA012JP was not formally designed to examine patients with early RA, nevertheless, the mean duration of RA in this study was 2.3 years, with a median of 2.0 years, therefore half of the patients enrolled met the RA duration criterion used in WA19926 to define an early population. The majority of patients in MRA012JP had active RA disease, as evidenced by comparison of the mean baseline mTSS scores which were considerably higher than those recorded in WA19926 patients.

Outcomes

Table 26. ACR20/50/70 Responses among Patients in WA19926 and Patients with Early RA in WA17824, at Week 24 (ITT)

	WA19926				WA17824 Early RA[a]	
	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	Placebo + MTX N=125	TCZ 8 mg/kg + Placebo N=116
ACR20 responders, n (%)	187 (65.2)	212 (73.6)[b]	216 (74.5)[c]	205 (70.2)	75 (60.0%)	85 (73.3%)
Weighted difference vs. MTX (95%CI)		0.09 (0.01, 0.16)	0.09 (0.02, 0.17)	0.05 (-0.02, 0.13)		0.16 (0.03, 0.28)
ACR50 responders, n (%)	124 (43.2)	138 (47.9)	165 (56.9)[c]	139 (47.6)	51 (40.8%)	62 (53.4%)
Weighted difference vs. MTX (95%CI)		0.05 (-0.03, 0.13)	0.14 (0.06, 0.22)	0.05 (-0.03, 0.13)		0.16 (0.03, 0.28)
ACR70 responders, n (%)	73 (25.4)	100 (34.7)[b]	112 (38.6)[c]	88 (30.1)	24 (19.2%)	41 (35.3%)
Weighted difference vs. MTX (95%CI)		0.09 (0.02, 0.17)	0.13 (0.06, 0.21)	0.05 (-0.02, 0.12)		0.16 (0.04, 0.29)

ITT = intent-to-treat population, RA = rheumatoid arthritis, MTX = methotrexate

[a] Patients in WA17824 who had ≤2 years RA at baseline

[b] $p < 0.05$; however, this comparison occurred after the break in hierarchical ordered testing sequence.

[c] $p < 0.05$.

Table 27. ACR/EULAR Remission at Week 12 and Week 24 among Patients in WA19926 and Patients with Early RA in WA17824 (ITT)

	WA19926				WA17824 Early RA[a]	
	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	Placebo + MTX N=125	TCZ 8 mg/kg + Placebo N=116
Week 12						
No. of Boolean Responders (%)	13/265 (4.9%)	29/273 (10.6%)	24/270 (8.9%)	25/279 (9.0%)	4/117 (3.4%)	11/110 (10.0%)
No. of Index Responders (%)	30/264 (11.4%)	42/271 (15.5%)	43/270 (15.9%)	42/278 (15.1%)	6/117 (5.1%)	13/110 (11.8%)
Week 24						
No. of Boolean Responders (%)	25/250 (10%)	43/257 (16.7%)	47/256 (18.4%)	38/267 (14.2%)	3/110 (2.7%)	13/104 (12.5%)
No. of Index Responders (%)	41/250 (16.4%)	58/257 (22.6%)	73/256 (28.5%)	60/266 (22.6%)	10/110 (9.1%)	23/104 (22.1%)

HAQ-DI = Health Assessment Questionnaire disability index, ITT = intent-to-treat population, RA = rheumatoid arthritis, MTX = methotrexate

[a] Patients in WA17824 who had ≤2 years RA at baseline

Study MRA012JP assessed inhibition of progression of structural joint damage in patients with RA with a disease duration of 6 months to 5 years.

Table 28. Changes in Modified Total Sharp Score, Erosion Score, and Joint Space Narrowing Score among Patients Receiving Monotherapy in WA19926 (ITT) and MRA012JP (FAS), at Week 52

	WA19926 (ITT)		MRA012JP (FAS) [a]	
	Placebo + MTX N=287	TCZ 8 mg/kg + Placebo N=292	Control (DMARD) N=143	TCZ 8 mg/kg N=157
Change from baseline to Week 52 in:				
Modified Total Sharp Score				
n	267	275	143	157
Mean (SD)	1.14 (4.30)	0.26 (1.88)	6.12	2.34
Modified Erosion Score				
n	267	275	143	157
Mean (SD)	0.63 (2.56)	0.15 (1.54)	3.21	0.85
Modified Joint Space Narrowing Score				
n	267	275	143	157
Mean (SD)	0.51 (2.36)	0.11 (1.05)	2.91	1.49
% Inhibition in mTSS at Week 52 in TCZ Group vs Placebo + MTX / Control [b]	-	77%	-	62%

FAS =full analysis set, ITT = intent-to-treat population, RA = rheumatoid arthritis, mTSS = Modified Total Sharp Score, MTX = methotrexate, SD = standard deviation

[a] Standard deviations were not calculated for these parameters in MRA012JP

[b] % inhibition is defined as 100 x (mean change from baseline in mTSS in Placebo + MTX or control group) – (mean change from baseline in mTSS in TCZ group) / (mean change from baseline in mTSS in Placebo + MTX or control).

Additional analyses

Long-term efficacy

Historical long-term efficacy data are provided from 3 data sets:

- LTE Early RA Subpopulation. The LTE All-Exposure population comprises 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, 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").
- LTE Monotherapy Subgroup. Long term efficacy data (cut-off date: 02 May 2012) were assessed from patients in study WA17824 who received TCZ monotherapy and continued on TCZ monotherapy up to 6.6 years in the LTE study WA18696 ("LTE monotherapy subgroup").
- Long-Term Patients in Study WA17823. Data up to Week 104 on prevention of structural joint damage were assessed for patients in Study WA17823, a Phase III study assessing the safety and prevention of structural joint damage during treatment with TCZ (8mg/kg or 4 mg/kg) + MTX versus placebo + MTX in patients with moderate to severe active RA who had an inadequate response to MTX (MTX-IR).

Outcomes

DAS28 Remission over Time in Early RA Patients

For patients with early RA (≤ 2 year duration) in the LTE early RA population maintenance of DAS28 remission (< 2.6) was assessed for up to 264 weeks.

Table 29. Maintenance of DAS28 Clinical Remission < 2.6 for Patients with Early RA (ITT)

DAS28 Clinical Remission	All TCZ (N = 805)
Week 48	
n	665
Maintained response for 24 weeks	148 (22.3%)
Week 96	
n	599
Maintained response for 24 weeks	214 (35.7%)
Maintained response for 48 weeks	151 (25.2%)
Week 144	
n	564
Maintained response for 24 weeks	227 (40.2%)
Maintained response for 48 weeks	167 (29.6%)
Maintained response for 96 weeks	109 (19.3%)
Week 192	
n	525
Maintained response for 24 weeks	237 (45.1%)
Maintained response for 48 weeks	180 (34.3%)
Maintained response for 96 weeks	120 (22.9%)
Maintained response for 144 weeks	81 (15.4%)
Week 264	
n	449
Maintained response for 24 weeks	188 (41.9%)
Maintained response for 48 weeks	159 (35.4%)
Maintained response for 96 weeks	121 (26.9%)
Maintained response for 144 weeks	89 (19.8%)
Maintained response for 192 weeks	71 (15.8%)

Remission: DAS28 < 2.6.
LOCF used for tender and swollen joint counts. No imputation used for ESR and Patients Global Assessment of Disease Activity VAS.
Where a DAS28 response can not be calculated, the patient will lose their response at that visit, therefore ending the period of maintenance.

DAS28 Remission over Time in Monotherapy RA Patients

For the WA17824 patients who continued to receive monotherapy TCZ treatment, maintenance of DAS28 remission (< 2.6) was assessed for up to 264 weeks.

Table 30. Maintenance of DAS28 Clinical Remission (<2.6) in Monotherapy RA Patients

DAS28 Clinical Remission	All TCZ (N = 135)
Week 48	
n	130
Maintained response for 24 weeks	32 (24.6%)
Week 96	
n	124
Maintained response for 24 weeks	44 (35.5%)
Maintained response for 48 weeks	33 (26.6%)
Week 144	
n	117
Maintained response for 24 weeks	50 (42.7%)
Maintained response for 48 weeks	41 (35.0%)
Maintained response for 96 weeks	26 (22.2%)
Week 192	
n	109
Maintained response for 24 weeks	49 (45.0%)
Maintained response for 48 weeks	31 (28.4%)
Maintained response for 96 weeks	24 (22.0%)
Maintained response for 144 weeks	16 (14.7%)
Week 264	
n	96
Maintained response for 24 weeks	40 (41.7%)
Maintained response for 48 weeks	36 (37.5%)
Maintained response for 96 weeks	25 (26.0%)
Maintained response for 144 weeks	17 (17.7%)
Maintained response for 192 weeks	14 (14.6%)

Remission: DAS28 < 2.6.
LOCF used for tender and swollen joint counts. No imputation used for ESR and Patients
Global Assessment of Disease Activity VAS.
Where a DAS28 response can not be calculated, the patient will lose their response at that
visit, therefore ending the period of maintenance.

ACR Responses in Patients Over Time

ACR20, ACR50, and ACR70 responses were measured in both the LTE early RA and monotherapy patient populations.

Table 31. Maintenance of ACR20, 50 and 70 Response by Visit for Patients with Early RA (ITT)

ACR20 / ACR50 / ACR70	All TCZ (N = 805)
ACR20	
Week 264	
n	449
Maintained response for 192 weeks	181 (40.3%)
ACR50	
Week 264	
n	449
Maintained response for 192 weeks	105 (23.4%)
ACR70	
Week 264	
n	449
Maintained response for 192 weeks	51 (11.4%)

LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted.
Source: etmainacr_ah023_durdis

Table 32. Maintenance of ACR20/50/70 Responses in Monotherapy RA Patients

ACR20 / ACR50 / ACR70	All TCZ (N = 805)
ACR20	
Week 264	
n	96
Maintained response for 192 weeks	58 (60.4%)
ACR50	
Week 264	
n	96
Maintained response for 192 weeks	40 (41.7%)
ACR70	
Week 264	
n	96
Maintained response for 192 weeks	15 (15.6%)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study WA19926 was a multi-centre, randomized, double-blind, and parallel-group study of the safety, disease remission and prevention of structural joint damage during treatment with tocilizumab, as a monotherapy and in combination with methotrexate, versus methotrexate in patients with early, moderate-to-severe rheumatoid arthritis.

The total study duration is 104 weeks. This submission was based on an interim analysis at week 52. The study is continuing in a blinded fashion into Year 2, and data from Week 104 will be reported at a later time. It has to be noted that such approach of interim analysis might jeopardise the further conduct of the blinded study and affect the integrity of study data in Year 2.

The target population for this study was adult patients with moderate-to-severe active early RA who were naïve to treatment with both MTX and a biologic agent.

The primary endpoint was the proportion of patients with disease remission, defined as DAS28 < 2.6, at Week 24. Disease remission as the primary endpoint is in line with the current treatment targets for early RA patients.

The sample size calculation is comprehensible and appropriate statistical methods were applied. However, from the sample size calculation in combination with the hierarchical testing procedure it appears that the interest in determining the effects of the TCZ 4 mg/kg + MTX group was relatively low.

There were two amendments of the protocol; which have no impact on the safety and efficacy analysis of the study.

The primary analysis population for efficacy was the intent-to-treat (ITT) population, which comprises all patients randomized into the study, provided at least one TCZ/placebo infusion was administered. Patients were assigned to treatment groups as randomized for analysis purposes.

The design e.g. patient population and endpoints is largely in line with the Points to consider on clinical investigation of medicinal products other than NSAIDS for treatment of rheumatoid arthritis (CPMP/EWP/556/95 rev 1/Final).

Treatment groups were balanced for the demographic characteristics sex, race, age, mean weight, height and mean body mass index (BMI). Slightly more patients in the placebo + MTX treatment group were non-Hispanic compared with the TCZ treatment groups (83% versus 76%−78%) and slightly fewer patients in the TCZ 8 mg/kg + MTX group who were postmenopausal compared with the other three treatment groups (37% versus 45% TCZ 4 mg/kg + MTX, 45% TCZ 8 mg/kg + placebo and 42% placebo + MTX). However, these differences are not considered clinically meaningful.

The treatment arms were well balanced with respect to RA disease characteristics. The mean and median duration of RA across treatment groups (0.4−0.5 years and 0.2−0.3 years, respectively) indicated that a very early RA population was recruited into the study. The overall oral corticosteroid use was also relatively low across all treatment arms. Slightly fewer patients in the TCZ 8 mg/kg + MTX group were using oral corticosteroids at baseline compared with the other three treatment groups. This difference is not considered clinically meaningful. The mean mTSS (Sharp-van der Heijde) was generally similar between all treatment groups at baseline. Of note, the mTSS observed at baseline were relatively low given that the target study population were patients with active, progressive RA, with erosions at baseline. This finding was consistent through all treatment groups. The low mTSS at baseline as well as the low percentage of patients using oral corticosteroids reflects suggests the inclusion of a very early treatment naïve RA population. The number of active joints elevated ESR or CRP, high HAQ-DI and VAS scores again indicated that the RA population recruited had active, progressive disease.

Efficacy data and additional analyses

The study met its primary endpoint of proportion of patients with DAS28 remission (DAS< 2.6) with the primary treatment comparison being the TCZ 8 mg/kg + MTX treatment group versus the placebo + MTX treatment group (44.8% versus 15.0%; OR = 4.77, 95% CI: 3.19 – 7.14; p < 0.0001). The

proportion of patients in DAS28 remission in the TCZ 4 mg/kg + MTX was numerically greater than in the placebo + MTX group (31.9% versus 15.0%; OR = 2.72;) however, this comparison fell after the hierarchical break in statistical testing.

A clear separation between TCZ 8 mg/kg + MTX and TCZ 8 mg/kg + placebo compared with the placebo + MTX group was apparent by Week 4; while for the TCZ 4 mg/kg + MTX a clear separation between TCZ 4 mg/kg + MTX and placebo + MTX group was apparent by Week 8. To assess the maintenance of the effect of the DAS28 remission, an exploratory analysis of the proportion of DAS28 remission responders at both Weeks 24 and 52 was performed. This showed that 79.2% of Week 24 responders were still a DAS28 responder at Week 52 in the TCZ 8 mg/kg + MTX group compared with 55.8% in the placebo + MTX group. In all, 70.8% of patients in the TCZ 8 mg/kg + placebo group maintained their response from Week 24 to Week 52 as did 76.1% of patients in the TCZ 4 mg/kg + MTX group.

This positive result for the TCZ 8 mg/kg + MTX treatment group was supported by a predefined set of secondary analyses, controlling for multiple testing.

It can be considered that early response is predictive to a certain extent for the treatment response to TCZ over time. The MAH is encouraged to attempt to determine baseline disease characteristics correlating with treatment response and maintenance of effect over time.

Since the initiation of the WA19926 study, ACR and EULAR have introduced more stringent remission measures, and therefore ACR/EULAR Boolean and Index remission as well as CDAI remission (CDAI data not shown) was added as exploratory endpoints in WA19926. Fewer patients in all treatment groups achieved remission using the newer endpoints, especially ACR/EULAR Boolean remission, which is the most stringent measure. This finding is consistent with observation from Kuriya at al. (J Rheumatol 2012; 39: 1155–8) indicating that frequency of remission in early RA differs according to the remission definition applied.

The ACR20, ACR50, ACR70 response rates were numerically higher for all TCZ groups in comparison with placebo + MTX, with the highest response rates seen in the TCZ 8 mg/kg + MTX group. Similar results were seen at Week 52.

TCZ treatment resulted in reduction of joint damage both in combination (8 mg/kg and 4 mg/kg) with MTX and as monotherapy, and this reduction was greater than achieved with MTX alone. This was shown in an exploratory analysis. The reduction of joint damage, was greater in all TCZ treatment groups of WA19926 compared to placebo + MTX at Week 52 as measured by lower change from baseline in mTSS, and Erosion and JSN scores. The differences in radiographic endpoints were statistically significant for the TCZ 8 mg/kg + MTX group compared with placebo +MTX.

The study was not designed to demonstrate the efficacy of the TCZ 4 mg/kg + MTX treatment in the hierarchical testing of the endpoints. However the data suggest that patients might experience a clinical benefit also for the lower TCZ dose. In the US, the recommended starting dose is 4 mg/kg IV followed by an increase to 8 mg/kg based on clinical response. In future, a comparative analysis of data from the EU and US registry could provide further information on the efficacy of the lower dose regimen. The MAH is encouraged to conduct such analysis when possible.

Of note, analysis of the exposure vs. DAS28 remission showed similar remission rates in quartile 3 and quartile 4 for patients treated with 8mg/kg, suggesting that these patients already in quartile 3 were on plateau in respect of efficacy.

The efficacy findings of study WA19926 were further supported by data from previous studies. Analysis of efficacy in the early RA subpopulation from study WA17824, and demonstrated the efficacy of TCZ at improving RA signs and symptoms in patients with early RA; e.g. the proportion of DAS28 remission

responders, the ACR20/50/70 response rates were consistently higher in TCZ-treated patients than in patients who received MTX.

Regarding the reduction of structural joint damage progression, the results observed in WA19926 are consistent with one year radiographic results from a subset of patients with early RA included in the Japanese TCZ monotherapy study MRA012JP.

Long-term data beyond Week 52 are not available for Study WA19926 yet. An analysis of long-term efficacy of TCZ in early RA patients was conducted on the all-exposure LTE data set. These data showed that early RA patients as well as patients treated with TCZ monotherapy, who continued to receive TCZ 8 mg/kg up to 6 years, could maintain clinical benefit for a prolonged period of time. The final Week 104 data for Study WA19926 are expected and the CHMP recommends submitting those date when available.

2.4.3. Conclusions on the clinical efficacy

The pivotal study met its target: The proportion of patients in DAS28 remission at Week 24 was significantly higher in the TCZ 8 mg/kg + MTX group than in the placebo + MTX group (44.8% versus 15.0%; OR = 4.77, 95%-CI: 3.19 – 7.14; p < 0.0001).

The study was not designed to formally demonstrate the efficacy of the TCZ 4 mg/kg + MTX treatment due to the hierarchical testing of the endpoints. Week 52 and preliminary week 104 data already showed that clinical benefit was also observed with the TCZ 4 mg/kg + MTX dose, although at lower rate than for the TCZ 8 mg +MTX group.

Exploratory analysis revealed that TCZ treatment results in reduction of joint damage both in combination (8 mg/kg and 4 mg/kg) with MTX and as monotherapy, and this reduction was greater than achieved with MTX alone.

An analysis of long-term efficacy of TCZ in early RA patients was conducted on the all-exposure LTE data set. These data showed that early RA patients as well as patients treated with TCZ monotherapy, who continued to receive TCZ 8 mg/kg up to 6 years, could maintain clinical benefit for a prolonged period of time.

2.5. Clinical safety

Patient exposure

The safety analysis population included all patients who received at least one TCZ/placebo infusion and had at least one post-dose safety assessment. Patients were assigned to treatment groups as treated. The 5 patients who did not receive any study drug and 4 patients who had no post-baseline safety data (3 [placebo + MTX] and 1 [TCZ 4 mg/kg + MTX]) were excluded from the safety population.

At the baseline visit, 2 patients randomized to the placebo + MTX group erroneously received one vial of TCZ during IV administration and were therefore allocated to the TCZ 4 mg/kg + MTX group for safety analysis. The total safety population comprised 1153 patients.

Table 33. Analysis Population by Actually Received Study Treatment (All Patients Population)

	PLACEBO + MTX	TCZ 4 MG/KG + MTX	TCZ 8 MG/KG + MTX	TCZ 8 MG/KG + PLACEBO	Treatment Not Received
No. of Patients Randomized	285	290	290	292	5
No. Included in SAFETY	282	289	290	292	0
No. Excluded from SAFETY	3	1	-	-	5
RECEIVED NO INFUSION OF I.V. STUDY TREATMENT (TCZ/PLACEBO) UP TO WEEK 24	-	-	-	-	5
NO SAFETY DATA POST BASELINE INFUSION	3	1	-	-	-

The majority of randomized patients completed 52 weeks of participation in the study (the median extent of exposure was 1.0 year), and were exposed to the planned cumulative dose of IV treatment (placebo or TCZ). The total number of PYs of exposure tocilizumab (the sum of the exposure to IV treatment for all patients) was similar across treatment groups (ranging between 249.2 and 260.6 PY).

Table 34. Exposure to IV Treatment (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.

Adverse events

The number of patients who experienced at least one AE was similar between TCZ and placebo + MTX treatment groups (88.3% [TCZ 8 mg/kg + MTX]; 85.6% [TCZ 8mg/kg + placebo]; 88.6% [4 mg/kg + MTX]; and 83.3% [placebo + MTX]). However, the total number of AEs was slightly higher in the TCZ 8mg/kg + MTX and TCZ 4kg/kg + MTX combination groups compared with TCZ 8 mg/kg monotherapy and placebo + MTX groups.

The rate of AEs (per 100-PY) in the TCZ + MTX combination therapy groups were also slightly higher than in the TCZ 8 mg/kg + placebo and placebo + MTX groups (434.1 [95% CI: 409.2, 460.0] TCZ 8 mg/kg + MTX; 394.1 [95% CI: 370.7, 418.5] TCZ 8 mg/kg + placebo; 444.3 [95% CI: 419.2, 470.5] TCZ 4 mg/kg + MTX; and 405.7 [95% CI: 381.3, 431.2] in the placebo + MTX group).

Table 35. AEs with an Incidence of at Least 3% by Preferred Term (Safety Population)

Adverse Event	PLACEBO + MTX N = 282 No. (%)	TCZ 4 MG/KG + MTX N = 289 No. (%)	TCZ 8 MG/KG + MTX N = 290 No. (%)	TCZ 8 MG/KG + PLACEBO N = 292 No. (%)
NAUSEA	46 (16.3)	41 (14.2)	43 (14.8)	19 (6.5)
UPPER RESPIRATORY TRACT INFECTION	41 (14.5)	37 (12.8)	30 (10.3)	39 (13.4)
ALANINE AMINOTRANSFERASE INCREASED	29 (10.3)	40 (13.8)	55 (19.0)	22 (7.5)
NASOPHARYNGITIS	38 (13.5)	40 (13.8)	28 (9.7)	27 (9.2)
TRANSAMINASES INCREASED	23 (8.2)	35 (12.1)	41 (14.1)	22 (7.5)
HYPERTENSION	21 (7.4)	16 (5.5)	23 (7.9)	26 (8.9)
DIARRHOEA	18 (6.4)	16 (5.5)	19 (6.6)	18 (6.2)
HEADACHE	12 (4.3)	20 (6.9)	18 (6.2)	20 (6.8)
DYSPEPSIA	16 (5.7)	17 (5.9)	11 (3.8)	14 (4.8)
RHEUMATOID ARTHRITIS	23 (8.2)	9 (3.1)	16 (5.5)	10 (3.4)
URINARY TRACT INFECTION	13 (4.6)	19 (6.6)	14 (4.8)	11 (3.8)
BRONCHITIS	6 (2.1)	18 (6.2)	20 (6.9)	8 (2.7)
MOUTH ULCERATION	12 (4.3)	14 (4.8)	14 (4.8)	10 (3.4)
ABDOMINAL PAIN UPPER	12 (4.3)	13 (4.5)	11 (3.8)	10 (3.4)
ASPARTATE AMINOTRANSFERASE INCREASED	8 (2.8)	9 (3.1)	17 (5.9)	11 (3.8)
BACK PAIN	7 (2.5)	10 (3.5)	8 (2.8)	19 (6.5)
VOMITING	13 (4.6)	13 (4.5)	14 (4.8)	4 (1.4)
SINUSITIS	9 (3.2)	12 (4.2)	11 (3.8)	11 (3.8)
ALOPECIA	14 (5.0)	14 (4.8)	7 (2.4)	6 (2.1)
RASH	3 (1.1)	18 (6.2)	12 (4.1)	8 (2.7)
COUGH	7 (2.5)	10 (3.5)	14 (4.8)	9 (3.1)
DIZZINESS	8 (2.8)	9 (3.1)	7 (2.4)	11 (3.8)
PHARYNGITIS	7 (2.5)	10 (3.5)	9 (3.1)	6 (2.1)
ARTHRALGIA	7 (2.5)	9 (3.1)	8 (2.8)	6 (2.1)
ORAL HERPES	11 (3.9)	12 (4.2)	3 (1.0)	4 (1.4)
OROPHARYNGEAL PAIN	9 (3.2)	8 (2.8)	6 (2.1)	7 (2.4)
GASTROENTERITIS	5 (1.8)	10 (3.5)	6 (2.1)	7 (2.4)
NEUTROPENIA	3 (1.1)	6 (2.1)	7 (2.4)	12 (4.1)
DEPRESSION	4 (1.4)	8 (2.8)	5 (1.7)	9 (3.1)
FATIGUE	5 (1.8)	7 (2.4)	9 (3.1)	5 (1.7)
INFLUENZA	5 (1.8)	9 (3.1)	5 (1.7)	4 (1.4)
PRURITUS	1 (0.4)	4 (1.4)	3 (1.0)	14 (4.8)
STOMATITIS	3 (1.1)	9 (3.1)	8 (2.8)	2 (0.7)
OEDEMA PERIPHERAL	-	6 (2.1)	6 (2.1)	9 (3.1)

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.

The highest AE rate per 100-PY was seen in the SOC of infections and infestations (highest rate for upper respiratory tract infection and nasopharyngitis), followed by gastrointestinal disorders (highest rates for nausea and diarrhoea), and investigations (highest rates for of aminotransferase and transaminase increase).

The rates of AEs (per 100-PY) considered by the investigator to be related (remotely, possibly, or probably related) to treatment were similar in TCZ 8 mg/kg + MTX and TCZ 4 mg/kg + MTX treatment groups (225.8 [95% CI: 208.0,244.7], and 232.0 [95% CI: 214.0,251.1], respectively); these rates were comparatively higher than the rates observed in the TCZ 8 mg/kg + placebo and placebo + MTX treatment groups (182.9 [95% CI:167.1,199.8] and 164.0 [95% CI: 148.6,180.5], respectively). The most frequently reported treatment-related AEs occurred in the SOCs of Infections and Infestations, followed by Gastrointestinal Disorders and Investigations.

Table 36. Rate of Adverse Events per 100 Patient Years by Intensity (Safety Population)

All body systems	PLACEBO + MTX (N=282) n [P100-PY]	TCZ 4 MG/KG + MTX (N=289) n [P100-PY]	TCZ 8 MG/KG + MTX (N=290) n [P100-PY]	TCZ 8 MG/KG + PLACEBO (N=292) n [P100-PY]
Mild				
Total Pts With at Least One AE	200	229	209	222
Total Number of AEs	661 [259.3]	739 [280.1]	678 [258.2]	707 [263.3]
95% CI for Rate	[239.9,279.9]	[260.3,301.1]	39.1,278.3]	[244.3,283.5]
Moderate				
Total Pts With at Least One AE	150	149	165	143
Total Number of AEs	339 [133.0]	383 [145.2]	429 [163.3]	326 [121.4]
95% CI for Rate	[119.2,147.9]	[131.0,160.5]	[148.3,179.6]	[108.6,135.3]
Severe				
Total Pts With at Least One AE	19	33	25	17
Total Number of AEs	34 [13.3]	50 [19.0]	33 [12.6]	25 [9.3]
95% CI for Rate	[9.2,18.6]	[14.1,25.0]	[8.6,17.6]	[6.0,13.7]

Investigator text for adverse events encoded using MedDRA version 15.0.
Multiple occurrences of the same adverse event in one individual are counted.
Patient Years Exposure refers to duration in study = the date of last safety assessment minus the date of the first oral/IV study medication dose + 1 day

The intensity of AEs was judged by the investigator to be mild, moderate, or severe. The majority of AEs (96%– 98% across all four treatment groups) were mild or moderate in intensity. A higher rate of moderate AEs in the TCZ 8 mg/kg +MTX group and a higher rate of severe AEs in the TCZ 4 mg/kg +MTX group were observed.

The most common SOCs in which severe AEs were reported were Infections and Infestations followed by Gastrointestinal Disorders and Investigations.

Serious adverse events, deaths, other significant events

Deaths

Nine deaths were reported up to Week 52 (2 [TCZ 8 mg/kg + MTX]; 1 [TCZ 8 mg/kg + placebo]; 4 [TCZ 4 mg/kg + MTX]; and 2 [placebo + MTX]).

Overall, the rate of deaths (per 100-PY) in the TCZ groups was similar to that seen in the placebo + MTX group, with the exception of the TCZ 4 mg/kg + MTX group. The slightly higher rate of deaths in the TCZ 4 mg/kg + MTX group compared with the other TCZ groups and placebo + MTX group was driven by a very small number of deaths.

The underlying cause of death was variable across treatment groups. Additionally, there was no pattern in the underlying cause of death in the TCZ 4 mg/kg + MTX group; however, three of the four deaths reported in this group occurred in patients who were > 80 years old.

Serious adverse events

The proportions of patients who experienced at least one SAE was similar between the study groups (10.7% [TCZ 8 mg/kg + MTX]; 8.6% [TCZ 8 mg/kg + placebo]; 10.0% [TCZ 4 mg/kg + MTX]; and 8.5% [placebo + MTX]). The rate of SAEs (per 100-PY) was slightly higher for the TCZ + MTX combination groups (13.3 [TCZ 8 mg/kg + MTX] and 15.9 [TCZ 4 mg/kg + MTX compared with 10.4 [TCZ 8 mg/kg + placebo] and 10.6 [placebo + MTX] groups).

The majority of SAEs were judged by the investigator as being unrelated to study treatment. A small proportion of patients had at least one related SAE (2.8% [TCZ 8 mg/kg + MTX]; 1.4% [TCZ 8 mg/kg + placebo]; 4.8% [TCZ 4 mg/kg + MTX]; and 2.1% [placebo + MTX]).

Infections and infestations were the most frequently reported SAEs followed by neoplasms, benign, malignant, and unspecified (including cysts and polyps), and respiratory, thoracic and mediastinal disorders.

Discontinuation due to adverse events and dose interruptions

In total, 149 patients withdrew prematurely from study treatment due to an AE (including SAEs).

The rates of AEs leading to withdrawal per 100-PY of exposure was higher in the TCZ treatment groups (TCZ 8 mg/kg + MTX: 22.5 [95% CI: 17.1, 29.0]; TCZ 8 mg/kg + placebo: 12.7 [95% CI: 8.8, 17.7]; TCZ 4 mg/kg + MTX: 13.3 [95% CI: 9.2, 18.5]) compared with placebo + MTX (8.2 [95% CI: 5.1, 12.6]).

The rate of AEs leading to withdrawal decreased over time for all treatment groups; and the majority were observed within the first 24 weeks of treatment in the TCZ treatment groups (TCZ 8 mg/kg + MTX, TCZ 8m/kg monotherapy, and TCZ 4 mg/kg + MTX) and within the first 12 week of treatment in the placebo + MTX group.

In all three TCZ treatment groups, the most common reasons for treatment discontinuation were attributed to the Investigations SOC, in particular events related to liver enzyme elevations (most common PTs in TCZ treatment groups: alanine aminotransferase increased [reported in 27 patients], transaminases increased [22 patients], and aspartate aminotransferase increased [4 patients]).

After investigations, infections were the most frequently reported reason for study withdrawal. A similar number of patients in each treatment group withdrew from the study due to an infection. There were 6 patients in the TCZ 8mg/kg + MTX group (2 patients withdrawn due to Herpes zoster, and 1 patients each withdrawn due to arthritis bacterial, cellulitis, Staphylococcal infection, or tuberculosis); 1 patient in the TCZ 8mg/kg + placebo group (withdrawn due to folliculitis); 4 patients in the TCZ 4mg/kg + MTX (withdrawn due to pneumonia, bronchopneumonia, lung infection, or urinary tract infection); and 4 patients in placebo + MTX (withdrawn due to pneumonia, pneumonia, influenza, sepsis, or tooth abscess).

Patients in all four treatment groups experienced dose modifications/interruptions due to AEs. The incidence was higher with TCZ combination therapy (171 of 290 patients [59.0%] in TCZ 8 mg/kg + MTX; 153 of 289 patients [52.9%] in TCZ 4 mg/kg + MTX) compared with placebo + MTX (134 of 282 patients [47.5%]); whereas, the incidence in TCZ 8 mg/kg + placebo (128 of 292 patients [43.8%] was lower than placebo + MTX.

The most common AEs leading to dose interruptions/modification were in the Investigations SOC (most frequently, alanine aminotransferase increased, transaminases increased, and aspartate aminotransferase increased), with the rate being highest in the TCZ 8 mg/kg + MTX group (48.4 per 100-PY [95% CI: 40.3, 57.5]), and lowest in the TCZ 8 mg/kg + placebo group (19.4 per 100-PY [95% CI: 14.5, 25.4]. The rate of Investigations AEs leading to dose modification/interruption was similar between TCZ 4 mg/kg + MTX and placebo + MTX (31.1 per 100-PY [95% CI: 24.7, 38.6], and 24.7 per 100-PY [195% CI: 9.0, 31.6]).

Infections and infestations were the next most frequent cause of dose interruptions/ modifications (with rates being similar across all groups, although numerically higher in the TCZ treatment groups), followed by gastrointestinal disorders (similarly common between TCZ 8 mg/kg + MTX, TCZ 4 mg/kg + MTX and placebo + MTX, with a lower rate in TCZ 8 mg/kg + placebo).

Adverse events of special interest

AESIs, predefined on the basis of findings from previous clinical studies, safety concerns for the RA population, as well as on the safety profile of other biologic agents used to treat RA, were: infections (including opportunistic infections), GI perforations, demyelinating disorders, hepatic events, myocardial infarction, stroke, malignancies, anaphylactic reactions, hypersensitivity, and bleeding events.

Table 37. 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

Infections and infestations were the most frequently reported AEs and SAEs in the study.

The overall incidence of infections was similar between the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, and placebo + MTX treatment groups; the incidence of infections in the TCZ 4 mg/kg + MTX group was numerically higher than the other groups. This same pattern was seen when rates were adjusted for exposure. Analysing infection rates by 12-week intervals revealed that for all treatment groups, rates were consistent over time and did not appear to increase with exposure.

The most common types of infections across all treatment groups were upper respiratory tract infections, nasopharyngitis, and urinary tract infections. The incidence of these infections in both TCZ 8 mg/kg treatment groups was similar to that observed in the placebo + MTX groups.

The majority of infections were of mild or moderate intensity. Infections of severe intensity were rare, but were more common in the TCZ 8 mg/kg + MTX and TCZ 4 mg/kg + MTX treatment groups compared with placebo + MTX (8 [TCZ 8 mg/kg + MTX], 6 [TCZ 8 mg/kg + placebo], 11 [TCZ 4 mg/kg + MTX], and 5 patients in the [placebo + MTX] group).

Serious infections were infrequent in all three TCZ treatment groups. Thirty-five serious infections were experienced by 35 patients in the safety population. Serious infections were more common in the TCZ treatment groups compared with placebo + MTX.

The most common serious infection was pneumonia. Serious pneumonias were most common in the TCZ 4 mg/kg + MTX group (6 patients [2.1%]); the incidence of serious pneumonias in TCZ 8 mg/kg + MTX (2 patients [0.7%]) and TCZ 8 mg/kg + placebo (1 patient [0.3%]) were similar to placebo + MTX (3 patients [1.1%].

There were five infections that led to death: lung neoplasm/pneumonia (TCZ 8 mg/kg + placebo), lung infection and pneumonia/malnutrition (TCZ 4 mg/kg + MTX), sepsis and pneumonia influenza (placebo + MTX).

No opportunistic infections were reported in this study up to Week 52.

One case of tuberculosis (TB) was reported in a 64-year-old female from Italy in the TCZ 8 mg/kg + MTX group (Patient 205655/17762). This was a new diagnosis of pulmonary TB, and the patient was reportedly exposed via her husband who had active TB.

Myocardial Infarction (MI)

The incidence of serious MI events in all treatment groups was low: 1 patient (0.3%) developed an MI in the TCZ 8 mg/kg + MTX group, 1 patient (0.3%) in the TCZ 8 mg/kg + placebo group, and 3 patients (1.0%) in the TCZ 4 mg/kg + MTX group. There were no MIs reported in the placebo + MTX treatment group.

Stroke

The incidence of serious stroke events in all treatment groups was low, with four events reported up to Week 52. Two patients (0.7%) had a stroke in the TCZ 4 mg/kg + MTX group, with an additional 2 patients (0.7%) who had a stroke in the placebo + MTX group. No strokes were reported for patients in the TCZ 8 mg/kg + MTX or TCZ 8 mg/kg + placebo treatment groups.

Malignancies

In total, 13 patients experienced 13 malignancies up to Week 52 of the study, with the incidence being similarly low across all treatment groups: 3 (1.0%) occurred in the TCZ 8 mg/kg + MTX group, 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 of these events were reported as non-serious AEs (two cases of basal cell carcinoma, one each in the TCZ 8 mg/kg + MTX and TCZ 8 mg/kg + placebo groups, and one case of breast cancer in situ in the TCZ 8 mg/kg + MTX group).

Five malignancies were also reported early in the study (prior to study Day 50).

Hypersensitivity AEs

Hypersensitivity reactions were identified as events that occurred during or within 24 hours of an infusion, excluding events that were not deemed unrelated to treatment. A conservative approach was taken to identify potential hypersensitivity reactions and this retrieval included all AEs, regardless of whether or not they were clinically consistent with hypersensitivity.

Potential hypersensitivity reactions were observed at a higher frequency in the TCZ treatment groups (TCZ 8 mg/kg + MTX: 17.6% [51 of 290 patients]; TCZ 8 mg/kg + placebo: 15.4% [45 of 292

patients]; TCZ 4 mg/kg + MTX: 20.4% [59 of 289 patients], compared with placebo + MTX (13.8% [39 of 282 patients])

Serious hypersensitivity / anaphylactic reactions

Serious hypersensitivity events were defined as SAEs that occurred during or within 24 hours of an infusion, excluding events that were not deemed to be unrelated to study treatment. Using this definition, the incidence was rare, with a total of 4 patients (1 patients [0.3%] in TCZ 8 mg/kg + MTX, 2 [0.7%] in TCZ 8 mg/kg + placebo, 1 [0.3%] in TCZ 4 mg/kg + MTX) experiencing four serious hypersensitivity events. Two of these were not clinically consistent with hypersensitivity (pneumococcal infection and increased transaminase). Excluding these there were 2 patients who experienced a serious hypersensitive. One patient was identified as having an anaphylactic reaction. This patient was negative for anti-TCZ antibodies in the confirmatory assay both at baseline and post-baseline. The second patient was reported to experience “infusion-related reaction”; the signs and symptoms were consistent anaphylactic reaction.

Bleeding Events

The incidence of serious bleeding events in all treatment groups was low, with six events experienced by 6 patients up to Week 52.

Serious bleeding events were not associated with low platelet counts. Two patients (0.7%) in the TCZ 8 mg/kg + MTX group, 1 patient (0.3%) in the TCZ 8 mg/kg + placebo group, 2 patients (0.7%) in the TCZ 4 mg/kg + MTX group and 1 patient (0.4%) in the placebo + MTX group reported a serious bleeding event.

Two of the bleeding events were a result of accidental falls Two of the events were GI haemorrhages (1 patient in the TCZ 8 mg/kg + MTX group had predisposing risk factors and 1 patient in placebo + MTX did not). One patient in the TCZ 4 mg/kg + MTX group died as the result of the bleeding event of cerebral haemorrhage.

Pregnancy

Seven cases of pregnancy were reported in the study up to Week 52.

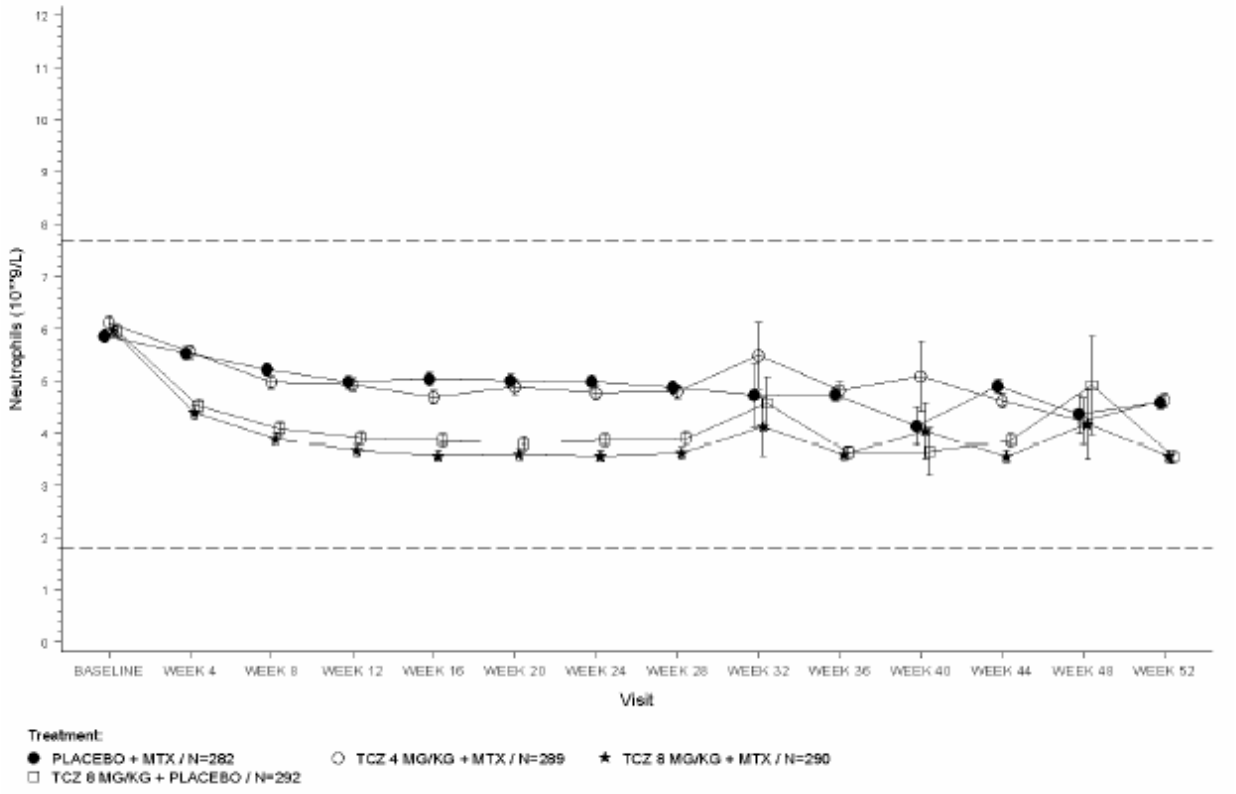
Three pregnancies were reported in the TCZ 8 mg/kg + MTX group, which resulted in patient discontinuation from treatment. Of the three cases, one case of pregnancy ended in spontaneous abortion (approximately 40 days into the pregnancy); two cases were ongoing at the time of data reporting.

Four pregnancies were reported in the TCZ 8 mg/kg + placebo group. Two cases of pregnancy resulted in discontinuation of study treatment; one case ended in a spontaneous abortion (duration of pregnancy was not known) and the other was still ongoing at the time of data reporting. Two cases of pregnancy resulted in in dosage modification; both cases ended in elective abortion (approximately 2 months and approximately 45 days into the pregnancy).

Laboratory findings

Neutropenia and abnormal neutrophil count

Figure 17. Mean (± SEM) Neutrophils Counts (109/L) by Visit (Safety Population)



Mean neutrophil counts were within normal range and similar between the TCZ treatment groups and the placebo + MTX group at baseline. In all groups (including placebo + MTX), there was a decrease in mean neutrophil levels after initiation of treatment that continued to Week 12. Thereafter neutrophil counts became relatively stable at levels below baseline values, but still within the normal range. The greatest changes were seen in the TCZ 8 mg/kg + MTX and TCZ 8 mg/kg + placebo groups, while the decrease observed in the TCZ 4 mg/kg + MTX group was similar to that in the placebo + MTX group.

Table 38. Worst NCI CTCAE Grades for Neutrophil Counts (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)
Neutrophils				
n	282	289	290	292
NORMAL	262 (92.9%)	245 (84.8%)	185 (63.8%)	206 (70.5%)
GRADE -1	13 (4.6%)	28 (9.7%)	52 (17.9%)	41 (14.0%)
GRADE -2	6 (2.1%)	14 (4.8%)	43 (14.8%)	36 (12.3%)
GRADE -3	1 (0.4%)	2 (0.7%)	10 (3.4%)	8 (2.7%)
GRADE -4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

Local analysis is excluded where central analysis is available on the same day.
CTC Grades Version 3.0.
Only non missing grades are included.

Neutrophil counts remained within normal range for 63.8% of patients in the TCZ 8 mg/kg + MTX group, 70.5% of patients in the TCZ 8 mg/kg + placebo group, 84.8% of patients in the TCZ 4 mg/kg + MTX group and 92.9% of patients in the placebo + MTX group. The majority of abnormalities

reported across all four treatment groups were Grade 1 and Grade 2 decreases. Grade 3 decreases were also observed in all treatment groups, but at a higher incidence in the TCZ 8 mg/kg + MTX and TCZ 8 mg/kg + placebo groups. The majority of Grade 3 decreases occurred at a single time point only. One Grade 4 decrease was observed in TCZ 8 mg/kg + placebo group.

There were 28 events of AEs defined as neutropenia in the study (7 [TCZ 8 mg/kg + MTX], 6 [TCZ 4 mg/kg + MTX], 12 [TCZ 8 mg/kg + placebo] and 3 [placebo + MTX]). These events of neutropenia were not associated with concurrent (defined as occurring within a 30-day window) serious infections, except for 1 patient in the TCZ 8 mg/kg + placebo group. The patient developed neutropenia on study Day 29 (neutrophil count 1.67 × 109/L) and subsequently developed an SAE of viral infection (manifesting as urticarial rash) on study Day 55. Study drug was temporarily interrupted and the patient's neutrophil levels normalized by study Day 71. The SAE resolved without sequelae and the patient continued in the study.

Six patients treated with MTX + placebo and 10 patients treated with TCZ 8 mg/kg + MTX, reported serious infections; none had low neutrophil counts occurring within 30 days of the infection.

Eleven patients treated with TCZ 4 mg/kg + MTX reported serious infections, of which, 3 patients had low neutrophil levels occurring at any time during the study, and 1 of these patients (pneumonia bacterial) had low neutrophils within 30 days of the SAE.

Eight patients treated with TCZ 8 mg/kg + placebo reported serious infections, of which 4 patients had low neutrophil levels occurring at any time during the study, and 2 of these patients had low neutrophils within 30 days of the event.

Platelet counts

Platelet counts remained within normal range for most patients in all treatment groups (90.8%–97.5% of patients across treatment groups)

Post-treatment, in platelet counts was observed in all treatment groups; however, the magnitude of change was more pronounced in the TCZ treatment groups compared with the placebo + MTX group.

There were 6 patients with AEs classified as thrombocytopenia in the study (2 [TCZ 8 mg/kg + MTX], 1 [TCZ 4 mg/kg + MTX], 2 [TCZ 8 mg/kg + placebo] and 1 [placebo + MTX]); none were associated with a bleeding event. None of the reported bleeding AEs were associated with platelet counts below the normal range.

Hepatic events and liver function test parameters

No serious hepatic events were reported.

Table 39. Transaminase and Total Bilirubin Shifts from Normal at Baseline to Worst Post-baseline Value (WA19926 Safety Population)

Parameter		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
Number (%) of patients with an increase from normal at baseline to >ULN to 3 × ULN[a]	ALT	104 (36.9)	113 (39.1)	141 (48.6)	104 (35.6)
	AST	84 (29.8)	79 (27.3)	131 (45.2)	84 (28.8)
	Bilirubin	8 (2.8)	18 (6.2)	40 (13.8)	26 (8.9)
Number (%) of patients with an increase from normal at baseline to >3 to 5 × ULN[a]	ALT	11 (3.9)	19 (6.6)	28 (9.7)	10 (3.4)
	AST	2 (0.7)	5 (1.7)	10 (3.4)	2 (0.7)
	Bilirubin	0 (0)	1 (0.3)	1 (0.3)	1 (0.3)
Number (%) of patients with an increase from normal at baseline to >5 × ULN[a]	ALT	2 (0.7)	6 (2.1)	9 (3.1)	4 (1.4)
	AST	0 (0)	1 (0.3)	5 (1.7)	2 (0.7)
	Bilirubin	0 (0)	0 (0)	0 (0)	1 (0.3)

[a] Excludes patients with missing values.
ULN: ALT = 55 U/l, AST = 40 U/l, Bilirubin = 17 µmol/l

After initiation of treatment there was an increase in mean ALT and AST levels in all four treatment groups. The majority of ALT/AST shifts from normal baseline levels in all three populations were from >ULN to ≤ 3 ×ULN.

Mean total bilirubin levels increased in all four treatment groups after initiation of treatment, but remained within the normal range throughout the study period.

Lipid parameters

Mean fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride concentrations were increased above baseline by the first assessment at Week 8 and remained stable thereafter at the higher level.

Analysis of LDL cholesterol levels according to the ATP III thresholds showed that the majority of patients maintained their baseline LDL cholesterol levels at the last observation. Increases in LDL cholesterol levels from < 160 mg/dL at baseline to ≥ 160 mg/dL at the last observation were more frequent in the TCZ treatment arms than in the placebo + MTX group. The greatest incidence of shifts to ≥160 mg/dL was observed in the TCZ 8 mg/kg + placebo group followed by the TCZ 8 mg/kg + MTX and the TCZ 4 mg/kg + MTX groups.

As with LDL cholesterol, the majority of patients maintained baseline total cholesterol levels at the last observation. The pattern of shifts in total cholesterol from levels < 240 mg/dL at baseline to ≥ 240 mg/dL at the last observation followed the same trend as that for LDL cholesterol.

Similarly, for HDL cholesterol, the majority of patients maintained baseline cholesterol levels at the last observation. However, the proportion of patients with baseline HDL levels in each ATP III category was more widely distributed, and approximately a third of all patients had baseline levels in the highest category of > 60 mg/dL. Increases from < 60 mg/dL at baseline to ≥ 60 mg/dL at the last observation were more frequent in the TCZ 8 mg/kg + MTX and TCZ 4 mg/kg + MTX groups than in the placebo + MTX and the TCZ 8 mg/kg + placebo groups.

The majority of patients maintained baseline triglycerides levels at last observation. The majority of patients had triglyceride levels in the lowest ATP III category of <150 mg/dL at baseline. Increases from <150 mg/dL to ≥150 mg/dL at the last observation were observed, with a greater incidence in the TCZ 8 mg/kg + placebo group followed by the TCZ 8 mg/kg + MTX group

Of the patients who were not taking lipid-lowering agents at baseline, the proportion of patients who initiated lipid-lowering treatments during the first 52 weeks of the study (including treatments in the

following classes: statins, fibrates and lipid regulating agents) was as follows: 3.9% on placebo + MTX, 3.5% on TCZ 4 mg/kg + MTX, 5.2% on TCZ 8 mg/kg + MTX, and 7.5% on TCZ 8 mg/kg + placebo.

Immunogenicity

During the 52-week treatment period, the percentage of patients who developed anti-TCZ antibodies (positive in both the screening and the confirmation assay post-baseline, and confirmation assay negative at baseline) was low (≤ 2.2%) and similar between the TCZ treatment groups (1.4% [TCZ 8 mg/kg + MTX], 1.1% [TCZ 8mg/kg + placebo] and 2.2% [TCZ 4 mg/kg + MTX]).

Additionally, 3.2% of the patients in the placebo + MTX group tested positive in the confirmation assay post-baseline (after negative confirmation assay results at baseline). Since patients in the placebo + MTX group had never been treated with TCZ, they could not have developed anti-TCZ antibodies and hence, these results are considered to be false positives. Please refer also to Clinical Pharmacology section of this report for detailed results and discussion on immunogenicity.

No patients with an anaphylactic reaction or severe hypersensitivity developed anti–TCZ antibodies.

Eleven patients in the TCZ treatment groups developed neutralizing anti-TCZ antibodies. None of them withdrew due to lack of efficacy or were classified as non-responders.

Further, no patient who withdrew due to lack of efficacy, or who was classified as having experienced loss of efficacy, developed neutralizing anti-TCZ antibodies.

Additional analysis

Adverse Events by C_{min} Exposure Quartiles at Week 24

The relationship between rates of all AEs and rates of infections and observed C_{min} at Week 24 was analysed and has been presented in PK section of this report. There was no clear trend for an increase in the incidence of total AEs or infections when C_{min} increased across quartiles, with the exception of a higher incidence rate for total AEs and infections in the fourth quartile of the TCZ 8 mg/kg + MTX group compared to the other quartiles in this group.

Preliminary Week 104 results from study WA19926

The preliminary Week 104 results for study WA19926 have been provided.

Table 40. Key Safety Data from the MTX-naïve Early RA Population of WA19926 at Weeks 52 and 104 and the Placebo Pooled DMARD-IR Population (Safety Population)

	MTX—Naïve Early RA Safety Population (Week 52)			MTX—Naïve Early RA Safety Population (Week 104)			Pooled Placebo—Controlled DMARD-IR Population		
	Placebo + MTX N = 282 254.89 PY	TCZ 4 mg/kg + MTX N = 289 263.79 PY	TCZ 8 mg/kg + MTX N = 290 262.64 PY	Placebo + MTX N = 282 339.53 PY	TCZ 4 mg/kg + MTX N = 289 394.64 PY	TCZ 8 mg/kg + MTX N = 527 718.39 PY	Placebo + DMARD N = 1010 542.63 PY	TCZ 4 mg/kg + MTX N = 611 426.78 PY	TCZ 8 mg/kg + DMARD N = 1407 841.45 PY
Pts with at least one AE (no. of events)	235 (1034)	256 (1172)	256 (1140)	244 (1249)	260 (1545)	456 (2418)	639 (1738)	461 (1491)	1040 (3402)
Rate per 100 PY (95% CI)	405.7 (381.3, 431.2)	444.3 (419.2, 470.5)	434.1 (409.2; 460.0)	367.9 (347.7, 388.8)	391.5 (372.2, 411.5)	336.6 (323.3, 350.3)	320.29 (305.41, 335.71	349.36 (331.85, 367.55)	404.30 (390.83, 418.12
Deaths	2	4	2	2	5	4	4	0	5
Rate per 100 PY (95% CI)	0.78 (0.10, 2.83)	1.52 (0.41; 3.88)	0.76 (0.09; 2.75)	0.59 (0.07, 2.13)	1.27 (0.41, 2.96)	0.56 (0.15, 1.43)	0.74 (0.20, 1.89)	0 (0, 0.86)	0.59 (0.19, 1.39)
Pts with at least one SAE (no. of events)	24 (27)	29 (42)	31 (35)	28 (31)	39 (58)	64 (83)	52 (61)	48 (55)	101 (121)
Rate per 100 PY (95% CI)	10.6 (7.0, 15.4)	15.9 (11.5; 21.5)	13.3 (9.3; 18.5)	9.1 (6.2, 13.0)	14.7 (11.2, 19.0)	11.6 (9.2, 14.3)	11.24 (8.60, 14.44)	12.89 (9.71, 16.77)	14.38 (11.93, 17.18)
Pts with Serious Infections (no. of events)	6 (6)	11 (11)	10 (10)	6 (6)	13 (16)	23 (25)	16 (17)	13 (15)	40 (43)
Rate per 100 PY (95% CI)	2.4 (0.9, 5.1)	4.2 (2.1, 7.5)	3.8 (1.8, 7.0)	1.8 (0.6, 3.8)	4.1 (2.3, 6.6)	3.5 (2.3, 5.1)	3.13 (1.83, 5.02)	3.51 (1.97, 5.80)	5.11 (3.70, 6.88)
Pts with Serious Myocardial Infarctions (no. of events)	0	3 (3)	1 (1)	0	3 (3)	2 (2)	2 (2)	1 (1)	2 (2)
Rate per 100 PY (95% CI)	0 (0, 1.45)	1.1 (0.2, 3.3)	0.4 (0.0, 2.1)	0 (0, 1.09)	0.8 (0.2, 2.2)	0.3 (0.0, 1.0)	0.37 (0.04, 1.33)	0.23 (0.01, 1.31)	0.24 (0.03, 0.86)
Serious Hepatic Events	0	0	0	0	0	0	0	0	0
Rate per 100 PY (95% CI)	0 (0, 1.45)	0 (0, 1.40)	0 (0, 1.40)	0 (0, 1.09)	0 (0, 0.93)	0 (0, 0.51)	0 (0, 0.68)	0 (0, 0.86)	0 (0, 0.44)

CI is based on events per 100 patient years.

Multiple occurrences of the same event in one individual are counted. Patient Years Exposure in this output refers to duration in study, calculated from first study drug intake to last safety assessment available + 1.

In the pooled DMARD-IR population, TCZ 4 mg/kg + MTX pooled Week 24/52 data from WA17822 and WA17823. TCZ 8 mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063.

Sources: WA19926 Week 52: staerate02_2, staerate07_2_ser, staerate07_5_sinfae, staerate01_2_drate, staerate07_2_mi_ser, staerate04_5_ser, staerate01_5_drate, staerate04_5, staerate04_5_ser_infae, staerate04_5_ser_mi DMARD-IR: STae_rate_ah001_all_dm, STae_rate_s_dm, STae_rate_sinf_dm, STrate_d_xesc_dm, STae_rate_shep_dm, STae_rate_smi_dm,

Post marketing experience

A summary of the post-marketing experience with TCZ based on safety data submitted previously in PSUR covering the period from 11 April 2005 up to 10 October 2012 the end of the reporting period for the most recent PSUR was provided. Since initial market approval in Japan on 11 April 2005 and until the end of the reporting period for the most recent periodic safety update report (PSUR), TCZ has been approved for use in over 100 countries, including the European Union and the United States of America.

During the period of the most recent PSUR, the estimated exposure to TCZ across all indications, via commercially obtained drug and through clinical trials, was 46,521 patients. The estimated cumulative exposure to TCZ since 11 April 2005, via commercially obtained drug and through clinical trials until 10 October 2012, was 184,398 patients.

At the data lock point of the latest PSUR, a cumulative total of 19,281 AE cases, involving 37,750 AEs had been recorded on the MAH's Global Safety Database. Of these, 9,776 cases, involving 21,264 AEs, were medically confirmed cases. These figures include spontaneously reported cases that had only non-serious listed events. Excluding such cases, a total of 8,435 medically-confirmed cases, involving 19,524 AEs, have been recorded.

During the reporting period for the latest PSUR, the marketing authorization holder received a total of 1,696 medically-confirmed cases containing 3,633 AEs. These events occurred in 1,689 patients. Of the 1,696 cases, 1,442 were serious with a total of 2,393 of the events categorized as SAEs. This figure of 1,696 medically-confirmed cases excludes spontaneous cases containing only non-serious listed events, of which there were 214 cases involving 257 AEs.

One hundred and ten fatal cases were received during the reporting period.

The most frequently reported AEs were within the SOCs “Infections and Infestations” (21.3% of total AEs), “General Disorders and Administration Site Conditions” (10.7% of total AEs), and “Gastrointestinal Disorder” (9.5% of total AEs).

2.5.1. Discussion on clinical safety

The safety assessment of TCZ in early RA is based on the pivotal Study WA19926. In this double blind placebo controlled study patients receiving two different doses of TCZ (8 mg/kg and 4 mg/kg) were evaluated in combination with MTX and the TCZ 8 mg/kg regimen was also evaluated as a monotherapy.

In the pivotal study the safety population included a total of 1153 patients; of these 871 patients received TCZ (all TCZ-population) and 282 patients received placebo. This corresponds to a cumulative exposure in study of 254.9 PY for the placebo group and of 794.9 PY for the All-TCZ population.

For a comparative analysis of the pooled TCZ patients in study WA19926 the following other RA safety populations are relevant:

- Controlled DMARD-IR population: pooled safety data from DMARD-IR patients from the placebo-controlled period of 3 studies: 24 weeks in WA17822 and WA18063, and 52 weeks in WA17823.
- Long Term Extension (LTE) All-exposure Population: the updated assessment of the ongoing LTE studies of IV TCZ in adult RA patients with a clinical data cut off of May 2012.
- LTE MTX-naïve subpopulation: LTE data from the subpopulation of patients who were MTX-naïve or who had not received MTX for 6 months prior to the core study WA17824.
- LTE early RA subpopulation: LTE data for patients starting TCZ with ≤ 2 years since their RA diagnosis.
- LTE monotherapy subgroup: LTE data from patients from the WA17824 study in which patients received TCZ monotherapy.

The rate of all AEs in Study WA19926 was higher than the corresponding rates for of all AEs in the LTE All-exposure population. However, in the initial 6 months of treatment for the LTE All-exposure population, this all AE rate was considerably higher (480.66 events per 100 PY [95% CI: 470.80, 490.69]) and more comparable to the rates observed in the WA19926 study (423.9 events per 100 PY [95% CI: 409.8, 438.5]). The same pattern of event rates vs. study WA19926 data was also seen for the LTE MTX-naïve and LTE early RA subpopulations and the LTE monotherapy subgroup. The rates of all AEs decreased over time in the LTE All-exposure population as well as in the various subpopulations (LTE MTX-naïve, LTE early RA, LTE monotherapy subgroup).

The majority of AEs (96% – 98% across all four treatment groups) were mild or moderate in intensity.

The most common AE was seen infections and infestations (highest rate for upper respiratory tract infection and nasopharyngitis), followed by gastrointestinal disorders (highest rates for nausea and diarrhoea), and investigations (highest rates for of aminotransferase and transaminase increase).

No new safety signals were detected in Study WA19926.

There were nine deaths reported up to Week 52 in Study WA1992; the rate of deaths (per 100-PY) in the TCZ groups was similar to that seen in the placebo + MTX group, however a slightly higher rate of deaths in the TCZ 4 mg/kg was observed. Overall the death rate observed in study WA19926 was slightly higher than that observed in the controlled DMARD-IR population, as well as the LTE All-Exposure, LTE MTX-naïve and LTE early RA populations, with the CIs overlapping.

The underlying cause of death in Study WA1992 was variable across treatment groups; no pattern in the cause of death was observed. Of note, three of the four deaths in the TCZ 4 mg group were reported in patients who were > 80 years old. This might suggest that inclusion of more vulnerable patients in the clinical study might have introduced a bias. Patients with current or previous (within past years) evidence of serious uncontrolled concomitant diseases (e.g. cardiovascular, pulmonary, endocrine) were excluded from the study. Furthermore patients with evidence of active malignant disease were also excluded from the study. The patient's narratives suggest that the exclusion criteria might not have been respected in this regard.

The proportions of patients in Study WA19926 who experienced at least one SAE was similar between the study groups. The rate of SAEs (per 100-PY) was slightly higher for the TCZ + MTX combination groups than for the placebo group; the CIs were overlapping. The majority of SAEs were judged by the investigator as being unrelated to study treatment. Infections and infestations were the most frequently reported SAEs followed by neoplasms, benign, malignant, and unspecified (including cysts and polyps), and respiratory, thoracic and mediastinal disorders.

The observed SAE rates in Study WA19926 were consistent with data reported in the DMARD-IR population in previous studies as well as with LTE data form IV TCZ studies. Consistent with data from these studies, the most frequent SOC affected by SAEs in the WA19926 was "Infections and Infestations". The other SOCs frequently affected with SAEs in study WA19926 also showed a similar pattern of distribution as was observed in other TCZ-treated populations.

Adverse events of special interest predefined on the basis of findings from previous clinical studies, safety concerns for the RA population, as well as on the safety profile of other biologic agents used to treat RA, were: infections (including opportunistic infections), GI perforations, demyelinating disorders, hepatic events, myocardial infarction, stroke, malignancies, anaphylactic reactions, hypersensitivity, and bleeding events.

The overall incidence of infections in Study WA19926 was similar between the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, and placebo + MTX treatment groups; the incidence of infections in the TCZ 4 mg/kg + MTX group was numerically higher than the other groups. Infection rates in study WA19926 were stable over the 52-week study period and did not appear to increase with exposure. This finding is consistent with the LTE data, suggesting there is no evidence of an increasing risk of infection over time with TCZ treatment.

Serious infections were infrequent in all three TCZ treatment groups. Serious infections were more common in the TCZ treatment groups compared with placebo + MTX. Overall, the pattern of serious infection rates in study WA19926 was similar to that previously observed in the controlled DMARD-IR population and LTE data.

No opportunistic infections were reported in this study up to Week 52.

The rate of serious hypersensitivity events in the All-TCZ group in study WA19926 was low and similar to the rates observed in the All-TCZ group in the controlled DMARD-IR population and in Month 0-6 of treatment in the LTE All-exposure population. The rate of anaphylaxis events in study WA19926 was

also low and again similar to that previously observed with TCZ treatment in both the controlled DMARD-IR population and the LTE All-exposure population.

Further events defined as events of special interest such as gastrointestinal perforation, demyelination disorders, hepatic events, myocardial infarction, stroke and bleeding events either did not occur or occurred at a low frequency in ALL-TCZ population in Study WA19926.

The types of AESIs reported in Study WA19926 are consistent with the known safety profile of TCZ.

In Study WA19926 in all groups (including placebo + MTX) there was a decrease in mean neutrophil levels after initiation of treatment that continued to Week 12. Thereafter neutrophil counts became relatively stable at levels below baseline values, but still within the normal range. The greatest changes were seen in the TCZ 8 mg/kg groups while the decrease observed in the TCZ 4 mg/kg group was similar to that in the placebo group. None of the patients with serious infections reported low neutrophil counts occurring within 30 days of the infection.

In Study WA19926 the percentage of patients who developed anti-TCZ antibodies (positive in both the screening and the confirmation assay post-baseline, and confirmation assay negative at baseline) was low. There was no relationship between anti-TCZ antibody development and clinical AEs in study WA19926. None of the patients in the TCZ treatment groups who developed neutralizing anti-TCZ antibodies withdrew due to lack of efficacy or were classified as non-responders.

The relationship between rates of all AEs and rates of infections and observed C_{min} at Week 24 was analysed. There was no clear trend for an increase in the incidence of total AEs or infections when C_{min} increased across quartiles, with the exception of a higher incidence rate for total AEs and infections in the fourth quartile of the TCZ 8 mg/kg + MTX group compared to the other quartiles in this group.

2.5.2. Conclusions on clinical safety

The unfavourable effects of TCZ are established and include infection, allergic reactions including anaphylaxis, neutropenia, and thrombocytopenia, AST/ALT/bilirubin elevation and hypercholesterolaemia. In general, the safety data from study WA19926 are consistent with the established safety profile of TCZ in adult RA.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC advice on the submitted Risk Management Plan: The PRAC considered that the risk management system version 16.0 could be acceptable with revisions required as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The MAH implemented the changes requested in the RMP by PRAC. The CHMP endorsed the updated Risk Management Plan (version 16.1) with the following content:

Safety concerns

Table 41. Summary of Ongoing Safety Concerns in Adults

Category	**Safety Concern**
Important Identified Risks	Serious infections
	Complications of diverticulitis
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Neutropenia and the potential risk of infection
	Thrombocytopenia and the potential risk of bleeding
	Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity
	Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events
	Malignancies
	Demyelinating disorders
	Immunogenicity
Missing information	Elderly Patients
	Pediatric patients
	Effects during pregnancy
	Hepatic impairment
	Renal impairment
	Combination with biologics
	Safety in patients <60 kg in switcher population
	Long-term safety in patients in the switcher patient population
	IgE data following TCZ SC treatment
Identified and potential interactions including food-drug and drug-drug interactions	CYP450 enzyme normalization

Table 42. Summary of Ongoing Safety Concerns in Paediatric Patients

Category	**Safety Concern**
Important Identified Risks	Serious Infections
	Serious hypersensitivity reactions
	Neutropenia
Important Potential Risks	Skeletal development
	Immunogenicity
	Malignancies
	CYP450 enzyme normalisation
Missing information	MAS in sJIA patients

Pharmacovigilance plan

Table 43. Table of Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
WA22479 (British Society of Rheumatology Biologics Register [BSRBR])	Prospective observational cohort studies for safety data collection.	General safety profile of TCZ. Safety of TCZ SC in patients < 60 kg in the switcher population. Long-term safety in switcher patient population.	Ongoing	Routine updates to be provided in the scheduled PSURs
WA22480 (ARTIS) registry study	To provide long term safety data from the use of TCZ in Sweden for RA patients			
GA28719 (RABBIT)	The long-term observation of treatment with biologics in RA (RABBIT) in German biologics registry			
Pregnancy registry (GA28720 [OTIS])	To evaluate pregnancy outcomes for women exposed to TCZ during pregnancy			
Paediatric Registry: Observational Safety and Effectiveness Study of Patients with Polyarticular Juvenile Idiopathic Arthritis Treated with Tocilizumab	To be finalized	Safety in paediatric patients	Protocol under assessment – opinion expected Q3 2014	Implementation date to be confirmed Q3 2014. Final CSR date expected August 2029.
WA18221 (sJIA)	Part I: to evaluate the efficacy and safety of TCZ in patients with active systemic juvenile idiopathic arthritis (sJIA); Part II: to examine the effect (in completers of Part I) of long term use of TCZ on: Safety (including immunogenicity) ; Efficacy (including assessment of joint counts and objective measurements including hsCRP, fever, hemoglobin); Ability to reduce corticosteroid dosage to clinically significant levels; Resumption of growth (as determined by	General safety profile of TCZ	Ongoing	Final CSR Q4 2014

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	growth velocity)			
WA28029	To evaluate decreased dose frequency in patients with sJIA who experience laboratory abnormalities during treatment with TCZ	Safety in paediatric patients	Ongoing	Projected first patient first visit June 2013 Final CSR 2016
NP25737	A pharmacokinetic and safety study of TCZ in patients less than 2 years old with active sJIA	Safety profile in paediatric patients less than 2 years old	Ongoing	November 2017
WA29049	Pharmacodynamics study to evaluate neutrophil kinetics and function following tocilizumab treatment in healthy volunteers	Neutropenia and the potential risk of infection	Study in set up phase	October 2014
NA25220	To assess: Efficacy of treatment with tocilizumab (TCZ) 162 mg SC versus placebo given every other week (q2w), in combination with DMARDs, at Week 24 using ACR20. Safety of treatment with TCZ 162 mg SC versus placebo given every other week (q2w), in combination with DMARDs, with regard to adverse events (AEs) and laboratory assessments. SECONDARY Prevention of progression of structural joint damage at Week 24 and Week 48 Improvement of physical function Long-term safety and efficacy Pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ following SC administration Immunogenicity of TCZ following SC administration.	Safety will be assessed using reporting of AEs, clinical laboratory results (haematology, chemistry, lipid profiles, liver function, immunogenicity [including IgE data], etc.), physical examination and vital signs.	Ongoing	Q3 2014

Risk minimisation measures

Table 44. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Serious Infections	SPC SPC Section 4.3 Contraindications Active, severe infections (see section 4.4) SPC section 4.4 Special warnings and precautions for use **Infections** Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8, Undesirable eEffects). RoActemra treatment should not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, and interstitial lung disease) which may predispose patients to infections. Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for moderate to severe RA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reactants. The effects of tocilizumab on C reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment. **Tuberculosis** As recommended for other biological treatments, RA sJIA and pJIA patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti mycobacterial therapy before initiating RoActemra.	Patient Alert Card To inform both the patient and health care providers that TCZ increases the risk of getting infections which can become serious if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of infections Patient Brochure To inform the patient of the risk of serious infections and and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide more detailed guidance to healthcare providers on the risk of serious infections

	Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with RoActemra. SPC section 4.8 Undesirable effects **Infections** In the 6-month controlled studies the rate of all infections reported with tocilizumab 8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD group. In the long term exposure population, the overall rate of infections with RoActemra was 108 events per 100 patient years exposure. In 6-month controlled clinical studies, the rate of serious infections with tocilizumab 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group. In the long term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported. **Interstitial Lung Disease** Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.	

	SPC SPC section 4.4 Special warnings and precautions for use **Infections** Vigilance…for moderate to severe RA, sJIA, or pJIA as signs and symptoms of acute inflammation… Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA and pJIA patients, should be instructed… **Tuberculosis** As recommended RA, sJIA, and pJIA patients should be screened for latent tuberculosis infection... Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with RoActemra <u>IV Actemra only</u> SPC section 4.8 Undesirable effects Paediatric population **sJIA :** **Infections** In the 12 week controlled phase, the rate of all infections in the tocilizumab group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the ongoing open label extension phase (Part II), the overall rate of infections remained similar at 306.6 per 100 patient years. In the 12 week controlled phase, the rate of serious infections in the tocilizumab group was 11.5 per 100 patient years. At one year in the ongoing open label extension phase the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media. **pJIA:** **Infections**	

	The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%). **Patient Information Leaflet:** **IV Formulation :** Section 2. What you need to know before you use RoActemra • You are not to be given RoActemra o if you have an active, severe infection. **SC Formulation:** Section 2. What you need to know before you are given RoActemra • Do not use RoActemra o if you have an active, severe infection. **Warnings and Precautions** If you have any kind of infection, short- or long-term, or if you often get infections. Tell your doctor immediately if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection. If you have had tuberculosis, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately. Section 4 Possible common serious side effects: tell a doctor. Infections: • fever and chills	

	• mouth or skin blisters • stomach ache If you notice any of these, tell your doctor as soon as possible.	
Complications of diverticulitis	SPC SPC section 4.4 Special warnings and precautions for use **Complications of diverticulitis** Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with RoActemra in RA patients (see section 4.8). RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation. SPC section 4.8 Undesirable effects **Gastrointestinal Perforation** During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess. **Patient Information Leaflet:** Section 2 Warnings and precautions Talk to your doctor or nurse before using RoActemra. If you have had intestinal ulcers or diverticulitis, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.	<u>Patient Alert Card</u> To inform both the patient and health care providers that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of such events. <u>Patient Brochure</u> To inform the patient of the risk of complications of diverticulitis and provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide more detailed guidance to healthcare providers on the risk of complications of diverticulitis
Serious Hypersensitivity Reactions	SPC SPC Section 4.8 Undesirable effects: **Infusion Reactions** In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of	<u>Patient Alert Card</u> To inform patients, parents or caregivers of pediatric patients, and health care providers that patients using

	patients in the tocilizumab 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting. The rate of anaphylactic reactions (occurring in a total of 8/4,009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with *intravenous*[2] tocilizumab (see section 4.4). SPC SPC section 4.4 Special warnings and precautions for use **Hypersensitivity Reactions** Serious hypersensitivity reactions, including anaphylaxis have been reported in association with RoActemra (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous treatment with tocilizumab even if they have received premedication with steroids and antihistamines. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of RoActemra should be stopped immediately, and appropriate therapy initiated and tocilizumab should be permanently discontinued. SPC Section 4.8 Undesirable effects Paediatric population sJIA : **Infusion Reactions** Infusion related reactions are defined as	RoActemra may develop allergic reactions during or after the infusion. Patients who develop allergic reactions after the infusion should seek medical attention immediately. <u>Patient Brochure</u> To inform the patient of the risk of of serious hypersensitivity reactions nd provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide guidance to healthcare providers on the risk of serious hypersensitivity reactions <u>Rheumatoid Arthritis Dosing Guide</u> To provide support to the patient and healthcare provider regarding dosing and administration instructions

[2] IV Formulation only

	all events occurring during or within 24 hours of an infusion. In the 12 week controlled phase, 4% of patients from the tocilizumab group experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment. In the 12 week controlled phase, 16% of patients in the tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the tocilizumab group, the events included, but were not limited to rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (< 1%) treated with tocilizumab during the controlled and up to and including the open label clinical trial. pJIA: **Infusion Reactions** In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occuring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8. No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported. Patient Information Leaflet (IV formulation): Section 2 What you need to know before you are given RoActemra. Warnings and precautions Talk to your doctor, or nurse before using	

	RoActemra: If you experience allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash during or after the infusion, then tell your doctor immediately. Patient Information Leaflet (SC formulation) : Section 2 What you need to know before you use RoActemra Warnings and precautions Talk to your doctor, pharmacist or nurse before using RoActemra. If you experience allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the injection, then tell your doctor immediately. Do not take the next dose until you have informed your doctor AND your doctor has told you to take the next dose if you have experienced any allergic reaction symptoms after RoActemra administration. Section 4 POSSIBLE SIDE EFFECTS Common side effects Rash and itching, hives Allergic (hypersensitivity) reactions.	
Neutropenia	SPC SPC section 4.4 Special warnings and precautions for use **Haematological abnormalities** Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 109/l. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 103/ µl). In patients who develop an ANC < 0.5 x 109/ l or a platelet count < 50 x 103/µl,	<u>Patient Brochure</u> To inform the patient of the risk of neutropenia and provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide guidance to healthcare providers on the risk of neutropenia

	continued treatment is not recommended. Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with RoActemra to date. In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2. SPC section 4.4 Special warnings and precautions for use (IV formulation) **Haematological abnormalities** In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2. SPC Section 4.8 Undesirable effects/Laboratory evaluations Haematological abnormalities **RA Patients** **Neutrophils** In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/ l occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/ l did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ l were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs. Infections with neutropenia have been reported. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.	

Paediatric population

pJIA Patients

Neutrophils

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1 × 10^9/L occurred in 3.7% of patients.

sJIA Patients

Neutrophils

During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1 x 109/l occurred in 7% of patients in the tocilizumab group, and no decreases in the placebo group.

In the ongoing open label extension phase, decreases in neutrophil counts below 1 x 109/l, occurred in 15% of the tocilizumab group.

SPC section 4.2 Posology and method of administration

RA Patients

Dose adjustments due to laboratory abnormalities (see section 4.4) (IV formulation)

- Low absolute neutrophil count (ANC)

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l.

Laboratory Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases > 1 x 10^9/ l resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue RoActemra

Dose adjustments due to laboratory abnormalities (see section 4.4) (SC

formulation)

Laboratory Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases > 1 x 10^9/ l resume dosing every other week and increase to every week injection, as clinically appropriate.
ANC < 0.5	Discontinue RoActemra

Paediatric patients:

sJIA Patients

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases > to > 1 x 10^9/ l resume RoActemra.
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in sJIA for a laboratory

	abnormality should be based on the medical assessment of the individual patient.	

pJIA Patients

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in pJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases to > 1 x 10^9/ l resume RoActemra.
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Patient Information Leaflet

Section 4 POSSIBLE SIDE EFFECTS

Common side effects: … low white blood counts shown by blood tests (neutropenia, leucopenia)

Important Potential Risks		
Neutropenia and the potential risk of infection	SPC SPC section 4.4 Special warnings and precautions for use Haematological abnormalities	Patient Brochure To inform the patient of the risk of neutropenia

	Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µl). In patients who develop an ANC < 0.5 x 10^9/ l or a platelet count < 50 x 10^3/µl, continued treatment is not recommended. Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with RoActemra to date. In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2. SPC Section 4.8 Undesirable effects/Laboratory evaluations Haematological abnormalities **Neutrophils** In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/ l occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/ l did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ l were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs. Infections with neutropenia have been reported. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical	and provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide guidance to healthcare providers on the risk of neutropenia

trials.

SPC section 4.2 Posology and method of administration / Dose adjustments due to laboratory abnormalities (see section 4.4) (SC formulation)

- Low absolute neutrophil count (ANC)

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l.

Laboratory Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases > 1 x 10^9/ l resume RoActemra dosing every other week and increase to every week injection, as clinically appropriate
ANC < 0.5	Discontinue RoActemra

SPC section 4.2 Posology and method of administration / Dose adjustments due to laboratory abnormalities (see section 4.4) (IV formulation)

Laboratory Value (cells x 10^9/ l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases > 1 x 10^9/ l resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue RoActemra

Paediatric patients:

sJIA Patients

SPC section 4.2 Posology and method of administration

sJIA Patients

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/ l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases to > 1 x 10^9/ l resume RoActemra
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

pJIA Patients

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in pJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/ l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases to > 1 x 10^9/ l resume RoActemra
ANC < 0.5	Discontinue RoActemra The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

SPC section 4.4 Special warnings and precautions for use

Haematological abnormalities

In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2.

SPC section 4.8 Undesirable effects

sJIA Patients

Neutrophils:

During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1 x 10^9/l occurred in 7% of patients in the tocilizumab group, and no decreases in the placebo group.

In the ongoing open label extension phase, decreases in neutrophil counts below 1 x 10^9/l, occurred in 15% of the tocilizumab group.

SPC section 4.8 Undesirable effects

pJIA Patients

Neutrophils

During routine laboratory monitoring in

	the tocilizumab all exposure population, a decrease in neutrophil count below 1 × 10^9/L occurred in 3.7% of patients. Patient Information Leaflet Section 4 POSSIBLE SIDE EFFECTS Common side effects: … low white blood counts shown by blood tests (neutropenia, leucopenia)	
Thrombocytopenia and the potential risk of bleeding	SPC SPC section 4.4 Special warnings and precautions for use **RA** **Haematological abnormalities** Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2. SPC Section 4.8 Undesirable effects **Haematological abnormalities** Platelets In the 6-month controlled trials decreases in platelet counts below 100 x 103/ µl occurred in 1.7% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials. SPC section 4.2 Posology and method of administration (IV formulation) <u>Dose adjustments due to laboratory</u>	<u>Patient Brochure</u> To inform the patient of the risk of thrombocytopenia and provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide guidance to healthcare providers on the risk of thrombocytopenia

abnormalities (see section 4.4)

- Low platelet count

Laboratory Value (cells x 10^3/ µl)	Action
50 to 100	Interrupt RoActemra dosing When platelet count > 100 x 10^3/ µl resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue RoActemra

SPC section 4.2 Posology and method of administration (SC formulation)

Dose adjustments due to laboratory abnormalities (see section 4.4)

- Low platelet count

Laboratory Value (cells x 10^3/ µl)	Action
50 to 100	Interrupt RoActemra dosing. When platelet count > 100 x 10^3/ µl resume RoActemra dosing every other week and increase to every week injection as clinically appropriate.
< 50	Discontinue RoActemra.

Paediatric patients:

SPC section 4.4 Special warnings and precautions for use (IV formulation)

Haematological abnormalities

In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see

	section 4.2. SPC section 4.8 Undesirable effects (IV formulation) **Platelets** sJIA Patients During routine laboratory monitoring in the 12 week controlled phase, 3% of patients in the placebo group and 1% in the tocilizumab group had a decrease in platelet count to ≤ 100 x 10^3/µl. In the ongoing open label extension phase, decreases in platelet counts below 100 x 10^3/µl, occurred in 3% of patients in the tocilizumab group, without associated bleeding events. pJIA Patients During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to ≤ 50 × 103/µL without associated bleeding events.	
Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity	SPC SPC section 4.4 Special warnings and precautions for use **Active hepatic disease and hepatic impairment** Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8). **Hepatic transaminase elevations** In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, without progression to hepatic injury (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be	<u>Patient Brochure</u> To inform the patient of the risk of liver enzyme and bilirubin elevations and provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide guidance to healthcare providers on the risk of liver enzyme and bilirubin elevations.

	considered. Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended. In RA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, RoActemra treatment should be interrupted. SPC section 4.8 Undesirable effects **Hepatic transaminase elevations** During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs. The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 2 x ULN.	

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

SPC section 4.2 Posology and method of administration (IV formulation)

Dose adjustments due to laboratory abnormalities (see section 4.4)

Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, reduce RoActemra dose to 4 mg/kg or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate
> 3 to 5 x ULN (confirmed by repeat testing, see section 4.4).	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN, discontinue RoActemra
> 5 x ULN	Discontinue RoActemra

SPC section 4.2 Posology and method of administration (SC formulation)

Dose adjustments due to laboratory abnormalities (see section 4.4)

Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x	Dose modify concomitant

Upper Limit of Normal (ULN)	DMARDs if appropriate. For persistent increases in this range, reduce RoActemra dose frequency to every other week injection or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised. Restart with weekly or every other week injection, as clinically appropriate.
> 3 to 5 x ULN	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN. For persistent increases > 3 x ULN (confirmed by repeat testing, see 4.4.), discontinue RoActemra.
> 5 x ULN	Discontinue RoActemra.

Peadiatric Patients

SPC section 4.4 Special warnings and precautions for use

Hepatic transaminase elevations

In sJIA and pJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.

sJIA Patients

SPC section 4.8 Undesirable effects

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST ≥ 3 x ULN occurred in 5% and 3% of patients, respectively, in the tocilizumab group, and 0% in the placebo group.

In the ongoing open label extension phase, elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients, respectively, in the tocilizumab group.

pJIA Patients

	During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥ 3xULN occurred in 3.7% and <1% of patients, respectively. Patient Information Leaflet (IV formulation) Section 2 Warning and precautions If you have liver disease, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function. Patient Information Leaflet (SC formulation) Section 2 Warning and precautions If you have liver disease, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.	
Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	SPC SPC section 4.4 Special warnings and precautions for use **Lipid parameters** Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with tocilizumab (see section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents. **RA Patients** In RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. **Cardiovascular Risk** RA patients have an increased risk for	Patient Brochure To inform the patient of the risk of elevated lipid levels and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of elevated lipid levels

	cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care. SPC section 4.8 Undesirable effects **Lipid parameters** During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ l. Elevations in lipid parameters responded to treatment with lipid-lowering agents. During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials. <u>RA Patients</u> SPC section 4.8 Undesirable effects Hypertension reported as a common ADR. **Paediatric Patients** SPC section 4.4 Special warnings and precautions for use **Lipid parameters** In sJIA, pJIA and RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. SPC section 4.8 Undesirable effects **Lipid parameters**	

	sJIA: During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol > 1.5 x ULN to 2 x ULN occurred in 1.5% of the tocilizumab group and none in the placebo group. Elevation in LDL > 1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the tocilizumab group, and in 0% of the placebo group. In the ongoing open label extension phase, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled phase data. pJIA: During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x ULN in one patient (0.5%). Patient Information Leaflet Section 2 Warnings and precautions If you have cardiovascular risk factors such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.	
Malignancies	SPC SPC section 4.4 Special warnings and precautions for use **RA Patients** **Malignancy** The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. SPC section 4.8 Undesirable effects **Malignancies** The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.	<u>Patient Brochure</u> To inform the patient of the risk of malignancies and provide additional guidance beyond that provided in the PIL <u>Healthcare Provider Brochure</u> To inform and provide guidance to healthcare providers on the risk of malignancies
Demyelinating disorders	SPC	<u>Healthcare Provider</u>

	SPC section 4.4 Special warnings and precautions for use **Neurological disorders** Physicians should be vigilant for symptoms potentially indicative of new onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.	<u>Brochure</u> To inform and provide guidance to healthcare providers on the risk of demyelinating disorders
Immunogenicity	SPC SPC section 4 .8. Undesirable effects **RA Patients** **Immunogenicity** A total of 2,876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies. In SC-I, a total of 625 patients treated with tocilizumab 162 mg weekly were tested for anti-tocilizumab antibodies in the 6-month controlled period. Five patients (0.8%) developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies. One patient was tested positive for IgE isotype (0.2%). In SC-II, a total of 434 patients treated with tocilizumab 162mg every other weekly were tested for anti-tocilizumab antibodies in the 6-month controlled period. Seven patients (1.6%) developed positive anti-tocilizumab antibodies; of these, six (1.4%) developed neutralizing anti-tocilizumab antibodies. Four patients were tested positive for IgE isotype (0.9%). No correlation of antibody development to clinical response or adverse events was observed. SPC section 4 .8. Undesirable effects (IV formulation) sJIA Patients **Immunogenicity** All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-	None proposed

	tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-tocilizumab antibody formation might be underestimated because of interference of tocilizumab with the assay and higher drug concentration observed in children compared to adults. **pJIA Patients** One patient in the 10 mg/kg < 30kg group developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.	
Skeletal development (in paediatric patients)	None proposed	Not applicable
Missing Information		
CYP450 enzyme normalization	Routine risk minimization by means of labelling: SPC SPC section 4.5 Interaction with other medicinal products and other forms of interaction Interaction studies have only been performed in adults. Concomitant administration of a single dose of 10 mg/kg tocilizumab with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on tocilizumab clearance. The expression of hepatic CYP450 enzymes is suppressed by the cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as tocilizumab, is introduced. *In vitro* studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. Tocilizumab normalises expression of these enzymes. In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of tocilizumab, to the level similar to, or slightly higher than, those observed in healthy subjects.	None proposed

	When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy. Patient Information Leaflet (IV formulation) Section 2 What you need to know before you use RoActemra Other medicines and RoActemra Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. You, and parents/guardians of sJIA and pJIA patients should tell your doctor if you are using medicines containing any of the following active substances: • atorvastatin, used to reduce cholesterol levels • calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure • theophylline, used to treat asthma • warfarin/phenprocoumon, used as a blood thinning agent • phenytoin, used to treat convulsions • ciclosporin, used to suppress your immune system during organ transplants • benzodiazepines (e.g. temazepam), used to relieve anxiety Patient Information Leaflet (SC formulation) Section 2 What you need to know before you use RoActemra Other medicines and RoActemra Tell your doctor if you are taking , have recently taken or might take any other medicines. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, tell your doctor: • atorvastatin, used to reduce	

	cholesterol levels • calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure • theophylline, used to treat asthma • warfarin/phenprocoumon, used as a blood thinning agent • phenytoin, used to treat convulsions • ciclosporin, used to suppress your immune system during organ transplants • benzodiazepines (e.g. temazepam), used to relieve anxiety	
Macrophage Activation Syndrome in sJIA Patients	SPC Section 4.4 Special warnings and precautions for use (IV formulation) **Paediatric population** Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS. Patient Information Leaflet What you need to know before you are given RoActemra Section 2 Warnings and precautions If you have a history of macrophage activation syndrome, which is the activation and uncontrolled proliferation of specific blood cells, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.	<u>Patient Alert Card</u> To inform the patient of the risk of MAS and provide additional guidance beyond that provided in the PIL
Pediatric patients	SPC Section 4.2 Posology and method of administration **Special populations** **sJIA Patients** The safety and efficacy of RoActemra in children below 2 years of age has not been established. The recommended posology is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. Dose interruptions of tocilizumab for the following laboratory abnormalities are	None proposed

	recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient. **[Tables of dose modification recommendations]** Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in sJIA patients. Available data suggest that clinical improvement is observed within 6 weeks of initiation of reatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe. Section 4.4 Special warnings and precautions for use <u>Paediatric population</u> sJIA Patients Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS. Section 4.5: Interactions with other medicinal products <u>Paediatric population</u> Interaction studies have only been performed in adults. PIL <u>What RoActemra is and what it is used for and Children and Adolescents</u> RoActemra is not recommended for use in children younger than 2 years of age. <u>Children with SJIA</u> In general, the side effects in sJIA patients were similar in type to those seen in RA patients, listed above.	

Elderly Patients	SPC SPC section 4.2 Posology and Method of Administration Special populations *Elderly Patients* No dose adjustment is required in patients aged 65 years and older.	None proposed
Effects during pregnancy	SPC SPC section 4.6 Pregnancy and lactation Women of childbearing potential Women of childbearing potential must use effective contraception during and up to 3 months after treatment. Pregnancy There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown. RoActemra should not be used during pregnancy unless clearly necessary. Patient Information Leaflet Section 2 Pregnancy, breast feeding and fertility RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant. Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.	None proposed
Hepatic impairment	SPC SPC section 4.2 Posology and Method of Administration. Special populations Hepatic Impairment RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made. SPC section 4.4 Special warnings and precautions for use	None proposed

	Active hepatic disease and hepatic impairment Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8). SPC section 5.2 Pharmacokinetic properties <u>Special populations</u> Hepatic impairment : No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted. Patient Information Leaflet Section 2 Warnings and precautions Talk to your doctor, pharmacist, or nurse before using RoActemra: If you have liver disease, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.	
Renal Impairment	SPC SPC section 4.2 Posology and Method of Administration <u>Special populations</u> Renal Impairment No dose adjustment is required in patients with mild renal impairment. RoActemra has not been studied in patients with moderate to severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients. SPC section 5.2 Pharmacokinetic properties <u>Special populations</u> Renal Impairment No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 ml/min and ≥ 50 ml/min) did not impact the pharmacokinetics of tocilizumab.	None proposed

	Patient Information Leaflet Section 2 Warnings and precautions Talk to your doctor, pharmacist, or nurse before using RoActemra: If you have moderate to severe kidney function problems, your doctor will monitor you.	
Combination with biologics	SPC SPC section 4.4 Special warnings and precautions for use (IV formulation) Combination with TNF antagonists There is no experience with the use of RoActemra with TNF antagonists or other biological treatments for RA sJIA or pJIA patients. RoActemra is not recommended for use with other biological agents. SPC section 4.4 Special warnings and precautions for use (SC formulation) Combination with TNF antagonists There is no experience with the use of RoActemra with TNF antagonists or other biological treatments for RA, sJIA or pJIA patients. RoActemra is not recommended for use with other biological agents. Patient Information Leaflet (IV formulation) Section 2 Warnings and precautions Other medicines and RoActemra Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA, sJIA or pJIA. Patient Information Leaflet (SC formulation) Section 2 Warnings and precautions Other medicines and RoActemra Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA.	None proposed
Safety in patients <60 kg in switcher population	SPC SPC section 5.1 Pharmacodynamic properties Subcutaneous Use Clinical efficacy ... Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in	None proposed

	the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.	
Long-term safety in the switcher patient population	SPC SPC section 5.1 Pharmacodynamic properties Subcutaneous Use Clinical efficacy ... Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.	None proposed
IgE Data Following TCZ SC Treatment	SPC SPC section 4.8 Undesirable effects Subcutaneous Use Immunogenicity In SC-I, a total of 625 patients treated with tocilizumab 162mg weekly were tested for anti-tocilizumab antibodies in the 6 month controlled period. Five patients (0.8%) developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies. One patient was tested positive for IgE isotype (0.2%). In SC-II, a total of 434 patients treated with tocilizumab 162mg every other week were tested for anti-tocilizumab antibodies in the 6 month controlled period. Seven patients (1.6%) developed positive anti-tocilizumab antibodies; of these, six (1.4%) developed neutralizing anti-tocilizumab antibodies. Four patients were tested positive for IgE isotype (0.9%).	None proposed

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, for completeness phenprocoumon has been included in the list of medicines with individually adjusted posology that may require dose adjustment in SmPC section 4.5 and the statement on the paediatric population is included in SmPC section 4.9. Also, other editorial changes are implemented in SmPC sections 4.1, 4.4, 5.1, 10, Annex II and the PL.

Changes made to the PI in this procedure are shown in Attachment 1 (including also changes from procedure II/39, for which the CHMP Opinion is adopted in parallel).

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the pivotal study to evaluate the efficacy the primary endpoint was the proportion of patients with DAS28 remission (DAS28 < 2.6) with the primary treatment comparison being the TCZ 8 mg/kg + MTX treatment group versus the placebo + MTX treatment group. The study met its target: the proportion of patients in DAS28 remission at Week 24 was significantly higher in the TCZ 8 mg/kg + MTX group than in the placebo + MTX group (44.8% versus 15.0%; OR = 4.77, 95%-CI: 3.19 – 7.14; p < 0.0001). Also in other groups the DAS28 results were higher than in the Placebo + MTX group (38.7% in TCZ 8mg/kg + placebo group and 31.9% in TCZ 4 mg/kg + MTX group). Positive effect was observed also on other endpoints, including ACR20, ACR50, ACR70, mTSS.

Exploratory analysis revealed that TCZ treatment results in reduction of joint damage both in combination (8 mg/kg and 4 mg/kg) with MTX and as monotherapy, and this reduction was greater than achieved with MTX alone.

Uncertainty in the knowledge about the beneficial effects

An analysis of long-term efficacy of TCZ in early RA patients was conducted on the all-exposure LTE data set. These data showed that early RA patients as well as patients treated with TCZ monotherapy, who continued to receive TCZ 8 mg/kg up to 6 years, could maintain clinical benefit for a prolonged period of time.

The study was not designed to formally demonstrate the efficacy of the TCZ 4 mg/kg + MTX treatment due to the hierarchical testing of the endpoints. Week 52 and preliminary week 104 data already showed that clinical benefit was also observed with the TCZ 4 mg/kg + MTX dose, although at lower rate than for the TCZ 8 mg +MTX group. However there is some evidence that the lower dose has a less substantial effect of the inhibition of joint damage.

Risks

Unfavourable effects

The unfavourable effects of TCZ are established and include infection, allergic reactions including anaphylaxis, neutropenia, and thrombocytopenia, AST/ALT/bilirubin elevation and hypercholesterolaemia.

The proportions of patients in Study WA19926 who experienced at least one SAE was similar between the study groups. The rate of SAEs (per 100-PY) was slightly higher for the TCZ + MTX combination groups than for the placebo group. The majority of SAEs were judged by the investigator as being unrelated to study treatment. Infections and infestations were the most frequently reported SAEs

followed by neoplasms, benign, malignant, and unspecified (including cysts and polyps), and respiratory, thoracic and mediastinal disorders. The incidence of the AEs of special interest remained stable over time.

The observed SAE rates in Study WA19926 were consistent with data reported in the DMARD-IR population in previous studies as well as with LTE data form IV TCZ studies. Consistent with data from these studies, the most frequent SOC affected by SAEs in the WA19926 was “Infections and Infestations”. The other SOCs frequently affected with SAEs in study WA19926 also showed a similar pattern of distribution as was observed in other TCZ-treated populations.

Further events defined as events of special interest such as gastrointestinal perforation, demyelination disorders, hepatic events, myocardial infarction, stroke and bleeding events either did not occur or occurred at a low frequency in ALL-TCZ in Study WA19926.

The types of AESIs reported in Study WA19926 are consistent with the known safety profile of TCZ.

Uncertainty in the knowledge about the unfavourable effects

There was no clear trend for an increase in the incidence of total AEs or infections when C_{min} increased across quartiles, with the exception of a higher incidence rate for total AEs and infections in the fourth quartile of the TCZ 8 mg/kg + MTX group compared to the other quartiles in this group. However, the population size and the study duration were limited. Especially rare potential or identified risks such as infections including tuberculosis, complication of diverticulitis, immunological reactions, malignancies, and haematological abnormalities were not found.

In general, the preliminary Week 104 safety data for study WA19926 are consistent with the established safety profile of TCZ in adult RA. The rate of MIs in the WA19926 study is higher than that reported for the controlled DMARD-IR population and the LTE All-exposure population. The MI rate in study WA19926 has to be interpreted with caution, since it is based on a small number of events (6 events up to Week 104) study and the 95% CIs are overlapping between the populations. Moreover the data and are confounded by individual underlying risk factors at baseline. Furthermore, there is no biological plausibility that “first line RA patient” would experience more often MI than second line RA patients.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Rheumatoid arthritis is a chronic inflammatory and potentially disabling chronic systemic inflammatory disease, characterised by inflammation of the synovium leading to irreversible destruction of the joints and disability. Treatment goal is early remission, leading to sustained remission rates, improved physical function and health related quality of life, and limited radiographic damage.

TCZ is an established treatment option for patients with RA who have had an inadequate response to anti-TNFs or to non-biologic DMARDS. Study WA19926 demonstrated in treatment naïve RA patients, that TCZ in combination with MTX or alone resulted in higher percentages of patients achieving remission as measured by the DAS28 remission, ACR/EULAR Boolean and Index remission, and CDAI remission. A clinically relevant reduction of structural joint damage at Week 52 compared to MTX alone after treatment with TCZ 8 mg/kg or 4 mg/kg in combination with MTX and TCZ 8 mg/kg as a monotherapy.

The unfavourable effects of TCZ are established and include infection, gastro-intestinal disorders, infusion reactions, skin disorders, neutropenia, elevation in hepatic enzymes and lipid parameters.

Benefit-risk balance

The overall benefit-risk balance for RoActemra in treatment of severe, active and progressive RA in adults not previously treated with MTX is positive.

Discussion on the Benefit-Risk Balance

TCZ is an established treatment option for patients with RA who have had an inadequate response to anti-TNFs or to non-biologic DMARDS. Treatment naïve RA patients i.e. patients with early arthritis showed remission of symptoms and reduction of structural joint damage. The proportion of patients who responded to treatment was significant higher in the TCZ group than in the placebo group. The risks are well addressed in the SmPC and RMP.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

Extension of Indication to include treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC and the Package Leaflet are updated.

In addition, minor editorial changes are implemented in the SmPC, Annex II and PL.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.